



**CONTRACT NO. A833-057  
FINAL REPORT  
OCTOBER 1990**

**Incidence of Respiratory  
Symptoms and Chronic  
Diseases in a Non-Smoking Population  
as a Function of Long-Term Cumulative  
Exposure to Ambient Air Pollutants  
(AHSMOG Follow-Up Study)**

**State of California  
AIR RESOURCES BOARD  
Research Division**



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Final Report  
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October, 1990



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NON-SMOKING POPULATION AS A FUNCTION OF  
LONG TERM CUMULATIVE EXPOSURE TO  
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(AHSMOG FOLLOW-UP STUDY)**

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The statements and conclusions in this report are those of the Contractor and not necessarily those of the State Air Resources Board. The mention of commercial products, their source or their use in connection with material reported herein is not to be construed as actual or implied endorsement of such products.

## ABSTRACT

This report studies associations between long term cumulative ambient concentrations of air pollutants in a cohort of 6,340 non-smoking California Seventh-day Adventists. Average annual mean concentrations as well as hours in excess of different thresholds were estimated for each of total suspended particulates (TSP), ozone, and sulfur dioxide (SO<sub>2</sub>) using monthly interpolations from monitoring stations to zip code centroids from 1967 to 1987. Incidence of the following chronic diseases was ascertained: cancer, definite myocardial infarction (M.I.) (1977-1982); cumulative incidence of definite symptoms of airway obstructive disease, chronic bronchitis, and asthma (1977-1987). All natural cause mortality (1977-1986) was also ascertained. For several thresholds of TSP, statistically significant elevated relative risks were seen for all malignant neoplasms in females, definite symptoms of AOD, chronic bronchitis, and asthma. For one threshold of ozone (10 pphm) elevated relative risks were observed for incidence of respiratory cancers and asthma which approached but not quite achieved the 0.05 level of statistical significance. Increasing severity of asthma symptoms was statistically significantly related to two thresholds of ozone as well as mean concentration. SO<sub>2</sub> failed to show any statistically significant relationships with the health outcomes studied. Incidence of definite M.I. and all natural cause mortality failed to show statistically significant relationships with any of the pollutants studied.

## ACKNOWLEDGEMENTS

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Special mention must be made of the Adventist Health Study, funded by the National Cancer Institute, for their cooperation in providing all the lifestyle, cancer and ischemic heart disease incidence and mortality data collected from 1974 to 1982. Special thanks to Dr. Gary Fraser for assistance in the analysis of the cardiovascular disease data.

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## INTRODUCTION

This report consists of five papers, the first four of which have already been submitted for publication. Below we briefly summarize the findings of each paper and indicate their relationship to one another.

### Paper 1:

"Estimating Cumulative Ambient Concentrations of Air Pollutants. Description and Validation of Methods Used for an Epidemiological Study."

This paper describes the methods used for estimating cumulative ambient air pollution concentrations for study members. This paper describes the methods used to apply ambient concentrations of air pollutants monitored at fixed site stations in California to members of the study cohort according to their zip code by month residence histories. The methods for generating exceedance frequency statistics in excess of different thresholds are discussed. Results from a study which used monitoring stations as a receptor sites and interpolated from the surrounding monitoring stations is used to provide some insight as to the accuracy of the interpolation methods used for total suspended particulates and ozone. Correlations between actual versus interpolated two year mean concentrations were 0.78 for total suspended particulates and 0.80 to 0.90 for ozone. In order to evaluate the impact of the change from monitoring total oxidants to ozone on oxidant/ozone cumulations over past years, monthly mean concentrations for total oxidants were correlated to ozone for 435 station months for both pollutants were simultaneously monitored. The resulting correlation coefficient was 0.94.

### Paper 2:

"Ambient Air Pollution and Cancer in California Seventh-day Adventists (Long-Term Ambient Concentrations of Total Suspended Particulates and Oxidants as Related to Cancer Incidence and Mortality in California Seventh-day Adventists)."

This paper describes the relationships observed between TSP, ozone, and cancer incidence (1977-1982) and cancer mortality (1977-1986) in the study cohort of 6,340 non-smoking Seventh-day Adventist residents of California. Ambient concentrations were expressed in terms of both mean concentrations and exceedance frequencies, the numbers of hours during which ambient concentrations exceeded specified thresholds. Risk of malignant neoplasms in females, but not males, increased with increasing exceedance frequency for all TSP thresholds (100, 150, and 200 mcg/m<sup>3</sup>) except the lowest (60 mcg/m<sup>3</sup>). These increased risks were highly statistically significant. No statistically significant association was shown for mean concentration of TSP. Increased risk of respiratory cancer was associated with only one threshold of ozone (10 pphm), and this result was of borderline statistical significance due



to the small number of respiratory cancers, only 17 occurring in our study population.

Paper 3:

"Long Term Ambient Concentrations of Total Suspended Particulates and Ozone and Incidence of Respiratory Symptoms in a Non-Smoking Population."

This paper studies associations between total suspended particulates, ozone, and cumulative incidence of respiratory symptoms between 1977 and 1987 in a sub cohort of 3,914 individuals who completed the National Heart, Lung, and Blood Institute Respiratory Symptoms Questionnaire in 1977 and again in 1987. Increased risks of definite symptoms of airway obstructive disease and chronic bronchitis were associated with ambient hours in excess of total suspended particulates at thresholds of 100, 150, and 200 mcg/m<sup>3</sup> as well as mean concentration. Increased risk of asthma was associated with ambient hours in excess of thresholds of 150 and 200 mcg/m<sup>3</sup> but not mean concentration. Mean concentration and average annual exceedance frequencies for thresholds of 10, 12, 15, 20, or 25 pphm ozone were not statistically significantly associated with cumulative incidence of any of the respiratory symptoms outcomes, though a trend association (p=0.056) was noted between hours in excess of 10 pphm ozone and cumulative incidence of asthma. Analyses of cumulative incidence of respiratory symptoms excluded individuals who had definite symptoms in 1977. When these individuals were included in analyses which used change in a symptom severity score, mean concentration of ozone and average annual exceedance frequencies for thresholds of 10 pphm and 12 pphm were statistically significantly associated with change in severity of asthma. Change in severity for the other respiratory symptoms--AOD and chronic bronchitis were not significantly related to any of the thresholds of ozone or for mean concentration. It was felt that our study population lacks sufficient average annual hours of ambient concentrations above thresholds of 15 pphm and higher to detect significant associations with health outcomes with exceedance frequencies above these higher thresholds.

Paper 4:

"Long-Term Ambient Concentrations of Total Suspended Particulates and Oxidants as Related to Incidence of Chronic Disease in California Seventh-day Adventists."

This is a summary paper of all health outcomes covered in our study as related to TSP and ozone. It was presented at the International Society for Environmental Epidemiology Meetings in Berkeley in August and is subsequently being recommended for publication in Environmental Health Perspectives. The paper summarizes the findings of papers two and three above and extends results to include the health outcomes: all natural cause mortality and incidence of definite myocardial infarction (M.I.). No statistically significant associations were seen for all natural cause mortality or definite M.I. with TSP or ozone.

Except for describing the methods for ascertainment of incidence M.I. and all natural cause

mortality, the methods section of this paper is redundant with papers 1, 2, and 3 and the reader of this report may want to skip over it.

Paper 5:

"Long-Term Sulfur Dioxide Levels and Adverse Health Effects in Non-Smoking California Seventh-day Adventists."

This paper studies associations between ambient concentrations of sulfur dioxide (SO<sub>2</sub>) and all of the health outcomes included in this study--all malignant neoplasms, respiratory cancer, all natural cause mortality, incidence of definite myocardial infarction, cumulative ten year incidence of definite symptoms of airway obstructive disease, chronic bronchitis, and asthma. No statistically significant associations were seen between long-term ambient concentrations of SO<sub>2</sub> and any of these health outcomes. It was noted that mean ambient concentrations of SO<sub>2</sub> experienced by all our California study population were far lower than those of other epidemiological studies. It was felt that this was the most likely reason that no statistically significant associations between SO<sub>2</sub> and health outcomes were observed in this study.

As the methods for estimating cumulative ambient concentrations of SO<sub>2</sub> were the same as for TSP and ozone, the methods section of this paper is redundant with papers 1, 2, and 3, and the reader of this report may want to skip over it.

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**ESTIMATING CUMULATIVE AMBIENT CONCENTRATIONS OF AIR POLLUTANTS**

**DESCRIPTION AND VALIDATION OF METHODS USED  
FOR AN EPIDEMIOLOGICAL STUDY**

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## ABSTRACT

Methods for estimating cumulative ambient air pollution concentrations for individuals enrolled in an epidemiological cohort study are described and validated. The methods used monthly interpolations from fixed site monitoring stations in California to zip code centroids. Validation of the interpolation methods for total suspended particulates and ozone was conducted using fixed site monitoring stations in turn as receptor sites. Correlations between actual versus interpolated two year mean concentrations were 0.78 for total suspended particulates and 0.80 for ozone working hours - 8 a.m. to 5 p.m.; 0.90 for ozone home hours - 5 p.m. to 8 a.m. In order to evaluate the impact of the change from monitoring total oxidants to ozone on oxidant/ozone cumulations, monthly mean concentrations for total oxidants were correlated to ozone for 435 station months where both pollutants were simultaneously monitored. The resulting correlation coefficient was 0.94.

## INTRODUCTION

A question of increasing importance in environmental health is "What are the health effects of long-term (many years) ambient concentrations of community air pollutants?" One of the major difficulties in assessing such health effects is to compile an index which represents long-term cumulative ambient concentrations and which can be used for study participants in a free-living cohort study. The AHSMOG study is a prospective epidemiological cohort study of 6,301 non-smoking Seventh-day Adventists living from 10 to 21 years in areas of California which differ widely in levels of community air pollutants. Previous papers have shown statistically significant associations between prevalence of self-reported, definite symptoms of airway obstructive disease (AOD) and one or more thresholds of each of the pollutants: total suspended particulates (TSP), total oxidants (OX), and sulfur dioxide (SO<sub>2</sub>). Associations with nitrogen dioxide (NO<sub>2</sub>) were also studied but failed to show statistically significant associations (1,2). A methodological paper by Abbey et al. briefly described the methods for estimating long-term cumulative concentrations of air pollutants used for these studies and a technique for developing quantitative estimates of relative risks of disease above different threshold levels for the purpose of setting air quality standards (3). This paper describes updated and improved methods for estimating cumulative ambient concentrations of community air pollutants and describes validation studies which were conducted for total suspended particulates and oxidants/ozone to assess the accuracy of the interpolation methods. Future papers will address the associations between long-term (up to 21 years) cumulative ambient

concentrations of each of a number of air pollutants and incidence of each of a number of different chronic diseases. Air pollutants studied include total suspended particulates (TSP), total oxidants/ozone, sulfur dioxide, sulfates, and fine particulates. Chronic diseases studied include: incidence of respiratory cancers, all malignant neoplasms, congestive heart disease, and all natural cause mortality, as well as ten year cumulative incidence of a number of respiratory symptom complexes.

## METHODS

Ambient concentrations of air pollutants were estimated using fixed-site monitoring stations for which the California Air Resources Board (CARB) archives air quality data. Three hundred forty-eight of these stations were in the vicinity of the residences or work locations of study participants and were considered to have sufficiently complete data for at least one pollutant sometime in the years 1966-1987; only these stations were used in this study. One hundred twenty-six of these stations are located in the three air basins where most of the study participants lived -- the San Francisco Bay, South Coast, and San Diego air basins -- and 222 are located in the remainder of the state.

We defined "sufficiently complete data" for a station as at least ten months of representative data for one or more pollutants in each of three or more years. Routine monitoring of concentrations of TSP is for 24-hour periods (from midnight to midnight) every sixth day; a month of representative TSP data must have at least four 24-hour values (three for February). Hourly average ozone concentrations are monitored; to be representative, a month's ozone data must include at least 75% of the hourly averages.

Station-months which had less data for a pollutant were considered to have missing data.

TSP and ozone concentrations were monitored by methods satisfying the Environmental Protection Agency (EPA) standards in effect at the time of monitoring and are described in CARB monthly reports (for example (4)). The monitoring was supported by quality control and quality assurance programs meeting EPA standards.

So that health effects could be related to air quality standards, several thresholds were chosen for each pollutant corresponding to federal and state air quality standards as well as levels in between. The indices most used for assessment of long-term health effects were expressed as average annual hours for which ambient concentrations exceeded the thresholds. The average annual hours of excess concentration for each subject were calculated by a multi-step algorithm. The first step calculated for each monitoring station and month of representative data the number of hours during which concentrations exceeded each threshold. These monthly statistics will be referred to as exceedance frequencies.

The thresholds chosen for TSP included two of the national standards in effect at the time the study was being planned in 1986. (National standards for TSP were replaced by standards for 10 micron particulate matter in July, 1987.) The thresholds chosen for TSP were: 60 micrograms/cubic meter ( $\text{mcg}/\text{m}^3$ ), the national secondary standard for annual geometric mean; 100  $\text{mcg}/\text{m}^3$ , 150  $\text{mcg}/\text{m}^3$ , the national secondary 24-hour standard; and 200  $\text{mcg}/\text{m}^3$ . Our study areas lacked sufficient concentrations above the national primary 24-hour standard of 260  $\text{mcg}/\text{m}^3$  to warrant using it as a

threshold. For brevity, exceedance frequencies for the thresholds of TSP will subsequently be referred to as TSP60, TSP100, TSP150, and TSP200.

For ozone we used 10, 12, 15, 20 and 25 parts per hundred million (pphm) as the threshold levels; they correspond to 196, 235, 294, 392, and 490 mcg/m<sup>3</sup>, respectively. The first California standard for ozone in effect during the study period was 10 pphm total oxidants. This standard was subsequently restated as 10 pphm ozone, which remained the California standard for the remainder of the study period. The national primary standard is 12 pphm ozone. Exceedance frequencies for the thresholds of ozone will be referred to as OZ10, OZ12, OZ15, OZ20, and OZ25.

Ambient concentrations of TSP and ozone were estimated by the staff of the CARB. After calculating concentration statistics for each monitoring station for all months of representative TSP and ozone data, they interpolated these statistics to the centroids of the residence and workplace zip codes. Details of the calculation of concentration statistics and of the interpolations are discussed in the following paragraphs.

Exceedance frequencies for TSP were calculated for each month of representative data by counting the number of 24-hour monitoring periods with concentrations exceeding a threshold and multiplying this number by the ratios (days in month/number of monitoring periods with data in month), and finally multiplying by 24 to convert the exceedance frequency to hours for ease of comparison with exposures to gaseous pollutants. Exceedance frequencies for ozone were calculated by computing the percentage of hours during which the threshold was exceeded and then

multiplying this percentage by the number of hours in the month. Note that these algorithms automatically adjust for monitoring periods with missing data and that the adjustment assumes that the missing periods have the same distribution of concentrations as the periods with data.

Cumulative concentrations above a threshold were also represented by the "excess concentrations" above the threshold. Define the "excess concentration function" for a pollutant and threshold as the concentration minus the threshold if this difference is positive, and as zero otherwise. The month's excess concentration is the sum of the excess concentration function over all the month's monitoring periods. Excess concentrations were adjusted for missing data by the same rules used to adjust exceedance frequencies. Excess concentration statistics for TSP were also expressed in terms of hours to facilitate comparisons with gaseous pollutants; the units were microgram-hours per cubic meter. The units of excess concentrations of ozone were parts per hundred million-hours. The air pollution indices also included monthly mean concentrations, which may be alternatively defined as the excess concentrations above a zero threshold divided by the number of hours in the month.

Monthly exceedance frequencies and excess concentrations for residence and workplace zip codes occupied by the study population were computed by interpolation of these statistics from nearby monitoring stations. Statistics from up to three of the nearest stations satisfying the conditions set forth below were included in an interpolation. The statistics used in the interpolation were weighted by  $1/R^2$ , where R is the distance from the station to the zip code centroid. To be included in an



interpolation, a station must have satisfied the following conditions: be within 50 kilometers (31.25 miles) of the centroid; be on the same side of the barriers to airflow determined by Hayes et al. (5); and be on the same side of any other topographical obstructions to airflow rising more than 250 meters above the surrounding terrain.

The EPA has suggested categories of distances from stations within which the concentrations monitored at the stations may be considered representative (6). These categories vary with the pollutant. Stations in distance categories A and B of a point are respectively considered representative and moderately representative of concentrations at the point. More distant stations within 50 kilometers of the point are placed in category C. We assigned each interpolation a quality rating equal to the distance category of the nearest station. For TSP, mainly a primary pollutant, the distance categories are: A, within 3 miles; B, further than 3 miles but within 6 miles; C, more than 6 miles. For ozone, a secondary pollutant, the distance categories are: A, within 10 miles; B, further than 10 miles but within 20 miles; C, more than 20 miles.

A maximum of three stations were included in any interpolation. If any eligible station with an A or B quality rating had data, only stations with these ratings were included in the interpolation. Otherwise, data from stations with C ratings were used.

Separate monthly interpolations were used for work locations and home locations if the work location was more than 5 miles from the home location. Individuals were assumed to be at the work location from 8 a.m. to 5 p.m. on days which were not weekend days or federal holidays. There is hourly data for ozone, so that the exceedance frequencies and excess concentrations for the home location could be

calculated separately from those of the work location. For TSP, which is monitored for 24-hour periods, separate statistics for the month were calculated for the home location and for the work location. A weighted average of the home location and work location statistics was then computed, weighting by the assumed numbers of working and non-working hours in a month. If an individual's work location was missing for a month, the concentration statistics for his home location were used for the entire month.

Study participants sometimes resided for a month or more in areas outside the state of California or in areas within California which were not within 50 kilometers of a monitoring station. Such locations within California were manually examined by CARB staff who were knowledgeable about air pollution patterns throughout the state. By assigning these quality codes, we could later exclude individuals who had too much "assigned" data, if desired.

Locations affected by pollution transport from nearby polluted areas were assigned upper limit background exposures from these polluted areas and a quality rating of H. Locations in low-pollution rural areas not affected by transport were assigned zero background exposures and a quality rating of I.

Values for months with missing data were imputed by an algorithm which utilized values for the same zip code for nearby months in the same year or nearby years, depending upon the existence of non-missing data. These imputed values were assigned separate quality codes and were used for less than one percent of the person-months of exposure to ozone and TSP experienced by the population.

For locations outside California, exposures were coded as "possibly high" or

"low" according to whether or not the individual resided for that month within 50 kilometers of a city indicated by the EPA to have annual average exposure in excess of 60 mcg/m<sup>3</sup> for TSP, 14 parts/million for sulfur dioxide, or 12 parts/million ozone. Months with values coded as "possibly high" were considered to be missing, since there was insufficient data available to assign a quantitative value. Months with values coded as "low" were counted as zero exposures in excess of all thresholds, and a special quality code was assigned. Individuals who had no fixed location during a month or who did not report a residence for the month had those months coded as missing. In statistical analyses using cumulative concentrations, missing months were replaced by an individual's prior average cumulative concentration for the time period under consideration. This was done to avoid excluding from analyses those individuals who might be missing only a few months of data. Individuals with actual data for less than 80% of the months were excluded from all analyses. Thus, the imputation procedures for missing values described above were only used for individuals when 20% or fewer of the individual's monthly values were missing.

Individuals who were not excluded because of too much missing data had the following distribution of quality ratings for their person-months of TSP: quality A, 19.0%; quality B, 41.7%; quality C, 35.0%; H, 1.2%. Zero was assigned to 1.9% of person months according to the low or background ambient concentration codes as described above; 0.7% of person months were missing. For ozone the distribution of quality ratings for person months was: quality A, 89.8%; quality B, 5.4%; quality C, 1.8%; H, 0.6%. Zero was assigned to 1.9% according to the low or background ambient

concentration codes, and 0.5% of the person months had missing data.

Using the monthly residence and workplace zip codes obtained from respondents and the monthly pollution statistics interpolated to the zip codes, each individual's total cumulative exceedance frequency and excess concentration was calculated for each pollutant and threshold for each month from January 1966 to the earliest of: date of death, date of loss to follow-up, and April 1, 1987. Interpolated values since 1973 are considered to be more accurate, since a much larger network of operating stations has been operational since that time. Baseline cumulations were therefore calculated using the time period since January 1973, as well as the time period since January 1966. For most statistical analyses, the time period since January 1973 was used for cumulation. However, key analyses were repeated replacing statistics for this period with the cumulations since January 1966. The results reported were not sensitive to the choice of time periods for the baseline cumulations.

### **Results of Validation Studies**

A check on the validity of the computational methods used to generate cumulative exceedance frequencies and excess concentrations was made by comparing the statistics computed by two independently written sets of computer programs. The statistics were computed for 1973-1976 for a subgroup of 5,249 study participants residing in the South Coast Air Basin. Although the computer programs used slightly different methods of interpolation, all pairs of corresponding exceedance frequency and excess concentration statistics for both TSP and ozone had correlations greater than 0.9.

A check on the accuracy of the interpolation algorithms was performed by interpolating to monitoring stations from surrounding monitoring stations using the same interpolation algorithm. The actual monitored ambient concentration statistics at the stations and the statistics interpolated from surrounding monitoring stations were then compared. Since the purpose of this study is to assess the effects of long-term cumulations of ambient concentrations, the interpolated and actual values were each cumulated over two years, 1985 and 1986. The resultant two year cumulations were then compared using paired t-tests and correlation coefficients. For ozone, which is monitored hourly, cumulations were made for two separate time periods of the day: the "work" time period, 8 a.m. to 5 p.m. Monday-Friday except for holidays, and the "home" time period, all other hours. The results of the statistical comparisons are given in Table I. There were 142 stations for TSP and 126 stations for ozone which had one or more monitoring stations within interpolation range during the years 1985 and 1986. For this time period the distribution of quality ratings for station months was A, 9.6%; B, 21.9%; C, 68.4%; for ozone the distribution was A, 56.7%; B, 30.9%; C 12.4%. Interpolated values did not differ significantly from actual values, though there was a tendency for the interpolated values to average slightly higher than the actual values. Correlations between interpolated and actual values ranged from 0.60 to 0.92 except for TSP200, for which the correlation was 0.43. Lack of correlation between actual and estimated ambient concentrations of air pollution would tend to bias the statistical hypotheses tests of health effects towards the null hypothesis (7).

At the beginning of the study period, monitoring stations in California measured

total oxidants. Between 1973 and 1980, ozone monitors replaced the total oxidant monitors. The changeover was gradual, and some stations measured both total oxidants and ozone simultaneously for a period of time. Our study used ozone data whenever it was available and total oxidant data when ozone was not monitored. To assess the effects on the consistency of our data, we correlated the monthly exceedance frequency and mean concentration statistics for total oxidants and ozone for those station-months during which both oxidants and ozone were monitored. There were a total of 435 station-months during which both total oxidants and ozone were monitored concurrently in the years 1974-1979 with the number of different stations for a year ranging from 5 to 24.

Table II summarizes: (1) paired t-tests for the differences of population means of the monthly statistics for oxidant and ozone and (2) correlations between exceedance frequencies and mean concentration of the two pollutants. Monthly cumulations were first computed separately for working hours, and non-working hours; then t-tests and correlation coefficients were computed for the pooled data. Mean concentrations did not differ significantly, although each mean of an exceedance frequency for ozone was slightly higher than the corresponding mean for total oxidants, and the differences were statistically significant. Correlations between pairs of exposure indices for oxidants and ozone exceeded 0.90. Because of these high correlations, we felt justified in combining oxidant and ozone measures when cumulating over long time periods. In subsequent papers, we shall just refer to ozone, though some of the cumulations include total oxidant data from the time period when ozone was not measured.

## DISCUSSION

We have described methods for cumulating ambient concentrations of air pollutants over long periods of time in a manner which allows application of these ambient concentrations to an epidemiological cohort study. The methods allow interpolation of ambient concentrations to areas of study participants' work location and residence history, provided they are within representative distances from monitoring stations. Indices used to characterize cumulative concentrations incorporate thresholds to allow for direct application of epidemiological findings to existing air quality standards. The methods used facilitate application to a somewhat mobile human study population where mobility can be - both in terms of time periods within a day, such as work location and home location, as well as temporary or permanent relocation of worksite or residence. The methods incorporate ways of dealing with missing air pollution data as well as short-term missing residence history periods or short term stays in locations away from areas covered by interpolations from monitoring stations. The missing data methods incorporate quality rating flags so that sensitivity analyses can be conducted to determine the impact of missing data and poor quality data on epidemiological findings.

The question arises as to how valid the estimates of cumulative ambient concentrations are in relationship to the validity of measures of exposure used in other epidemiological studies such as studies of diet and cancer, exercise and cancer, etc. For assessment of such validity, the statistic which is often used is the Pearson's correlation between the crude measure and a more accurate measure. We will call this

correlation the "validity" correlation. It is generally recognized that in the context of epidemiological research where it is the relative ranking of the study population on the exposure variable being measured that is most important, the correlation coefficient is a more important guide than agreement of absolute quantitative values. Our validity correlations compare favorably with those of other epidemiological studies which range from 0.38 to 0.51 for exercise scales and 0.4 to 0.8 for dieting indices. (8-18)

The validity correlations which we observed in our validation study are probably a lower bound on what would be achieved for the actual study population due to the fact that the spacial distribution of monitoring stations available for the validity study was such that the interpolations had a higher percentage of the poorer C quality interpolations (68% for TSP and 12% for ozone) than did the interpolations actually used for the study population (35% for TSP and 2% for ozone).

There was an insufficient number of monitoring stations within each quality rating to allow adequate assessment of validity within each type of quality category. Quality ratings, however, are still valuable as they allow a sensitivity analyses to be incorporated when assessing associations with health effects.

The methods which have been described have sought only to estimate long-term ambient concentrations of air pollutants in the areas of work location or residence of study participants. They have not attempted to estimate actual exposure of study participants to these estimated ambient concentrations. Actual exposure would vary according to percent of time spent indoors, type of heating and air conditioning at home and at work, building penetration characteristics, indoor sources, etc. A number of



studies have sought to develop adjustment factors which could be applied to ambient concentrations or could take into account known indoor sources and thus be used for estimating exposures for various microenvironments. These factors are summarized by Winer (19) with application to the South Coast Air Basin where 2/3 of our study participants reside.

Future work will seek to adjust cumulative ambient concentration estimates for our population by incorporating some adjustment factors. Although such adjusted estimates may crudely represent exposure, to incorporate such adjustments will require many assumptions regarding the stability of lifestyle characteristics of study participants over time periods of up to 21 years.

We feel it is a useful check on such assumptions as well as other assumptions implicit in the modeling approach to relate health effects directly to estimated long-term ambient concentrations. In our analyses of health effects, indoor sources, such as cigarette smoking, which are especially relevant for TSP have been incorporated as covariates in the statistical models. Also, since the ambient concentrations are monitored for regulatory purposes it is useful to relate health effects ultimately to ambient concentrations.

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**Table 1.-Comparison of Actual Vs. Interpolated Two Year Cumulative Exceedance Frequencies And Mean Concentrations at Monitoring Stations For Total Suspended Particulates and Ozone for 1985 and 1986.**

<b>A. Total Suspended Particulates (n = 142 stations)</b>					
<u>Statistic</u>	<u>Actual Mean</u>	<u>Interpolated Mean</u>	<u>Paired t</u>	<u>p</u>	<u>Correlation</u>
Hrs > 60 mcg/m <sup>3</sup>	7827.5	8238.4	1.51	0.13	0.74
Hrs > 100 mcg/m <sup>3</sup>	2897.8	3166.0	1.38	0.17	0.75
Hrs > 150 mcg/m <sup>3</sup>	841.4	956.7	1.12	0.26	0.60
Hrs > 200 mcg/m <sup>3</sup>	279.5	336.1	1.12	0.27	0.43
Total Hrs. Mean Concentration mcg/m <sup>3</sup> for 2 yrs.	63.0	65.7	1.85	0.07	0.83
<b>B. Ozone (n = 126 stations)</b>					
<u>Statistic</u>	<u>Actual Mean</u>	<u>Interpolated Mean</u>	<u>Paired t</u>	<u>p</u>	<u>Correlation</u>
Hrs > 10 pphm					
Home:*	157.7	167.9	0.8	0.4	0.85
Work:**	126.2	127.2	0.1	0.9	0.81
Hrs > 12 pphm					
Home:*	87.6	96.9	1.1	0.3	0.85
Work:**	67.4	70.5	0.5	0.6	0.85
Hrs > 15 pphm					
Home:*	38.9	44.2	1.1	0.3	0.82
Work:**	28.3	30.5	0.8	0.5	0.86
Hrs > 20 pphm					
Home:*	9.3	10.4	0.7	0.5	0.76
Work:**	5.7	6.1	0.4	0.7	0.80
Hrs > 25 pphm					
Home:*	1.7	2.0	0.6	0.6	0.70
Work:**	0.9	0.9	0.2	0.8	0.63
Mean Concentration pphm					
Home:*	1.2	1.2	-0.3	0.8	0.92
Work:**	5.5	5.3	-1.7	0.09	0.80

\* Cumulations for "home" hours 5 p.m.-8.a.m. and all day weekends and holidays.  
 \*\* Cumulations for "work" hours 8 a.m.-5 p.m. weekdays, excluding holidays.

**Table 2.-Comparison of Monthly Cumulative Exceedance Frequencies, Excess Concentrations, and Mean Concentrations for Total Oxidants and Ozone for The 435 Station Months Where Both Were Simultaneously Monitored**

<u>Statistic</u>	<u>Total OX* Monthly Mean</u>	<u>Ozone* Monthly Mean</u>	<u>Paired t</u>	<u>p</u>	<u>Correlation</u>
Hours					
> 10 pphm	27.7	30.6	7.2	<0.001	0.98
> 12 pphm	20.0	22.7	7.4	<0.001	0.98
> 15 pphm	12.1	14.6	7.8	<0.001	0.97
> 20 pphm	4.9	6.5	6.6	<0.001	0.93
> 25 pphm	1.7	2.7	6.6	<0.001	0.90
Mean Concentration					
pphm	2.59	2.57	-0.81	0.42	0.94

**AMBIENT AIR POLLUTION AND CANCER  
IN CALIFORNIA SEVENTH-DAY ADVENTISTS**

**LONG-TERM AMBIENT CONCENTRATIONS OF TOTAL SUSPENDED  
PARTICULATES AND OXIDANTS AS RELATED TO  
CANCER INCIDENCE AND MORTALITY IN CALIFORNIA SEVENTH-DAY ADVENTISTS**

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## ABSTRACT

Cancer incidence and mortality in a cohort of six thousand non-smoking Seventh-day Adventist residents of California were monitored for a six-year period, and relationships with long-term ambient concentrations of total suspended particulates (TSP) and ozone (OZ) were modeled. Ambient concentrations were expressed in terms of both mean concentrations and exceedance frequencies, the numbers of hours during which concentrations exceed specified thresholds. The thresholds included federal and California air quality standards. Risk of malignant neoplasms in females increased with increasing exceedance frequency for all TSP thresholds except the lowest, and these increased risks were highly statistically significant. Increased risk of respiratory cancers was associated with only one threshold of OZ, and this result was of borderline significance. These results are presented in the context of setting standards for these two air pollutants.

## INTRODUCTION

Adverse health effects associated with ambient air pollution have been the subject of scrutiny by environmental scientists for a large part of the twentieth century (1,2). There is evidence that air pollution contributes to morbidity from airway obstructive disease and other forms of respiratory disease, cancer, and cardiovascular disease (3, 4). There is a considerable amount of difficulty in evaluating this evidence, however, because the effects of tobacco smoke are difficult to separate from the effects of air pollution, especially in urban areas where the numbers of smokers and concentrations of air pollutants are higher than in more rural areas. Cigarette smoking has been implicated in the etiology of cardiovascular disease, respiratory diseases, lung cancer, and several other forms of cancer in humans (e.g., cancers of the bladder and pancreas).

The great majority of the studies of air pollution and cancer in humans have been epidemiologic investigations utilizing the cross-sectional or correlational design (5, 6). In this approach, indices of air pollution in certain geographic locales have been correlated with the age-adjusted cancer mortality rates in the same areas, with or without adjustment for consumption of cigarettes. Most of these studies have not demonstrated increased cancer risk with increasing levels of air pollution. However, in many instances this inability to detect relationships may have been due to limitations in study design, poor statistical power, or other methodological weaknesses.

Seventh-day Adventists provide a unique opportunity for investigating the health effects of ambient air pollutants with very little confounding by tobacco smoke. By

church proscription, Seventh-day Adventists do not use tobacco or alcohol. They do, however, differ widely in their contact with ambient air pollution by virtue of their choice of residence and occupation. This variability in pollution exposure makes possible the evaluation of the relationship between exposure and health effects with very little confounding by tobacco smoke.

In this report we present the risks of cancer associated with long-term exposure to ambient concentrations of total suspended particulates (TSP) and ozone (O<sub>3</sub>) which were observed in a cohort study of non-smoking California Seventh-day Adventists.

## METHODS

The study design and measurement of ambient air pollution have been described in the previous paper (7).

### Enrollment of the study population.

In April of 1977, a subgroup of 6,340 members of the National Cancer Institute-funded Adventist Health Study were enrolled in a prospective epidemiological study for the primary purpose of studying the health effects of long-term cumulative contact with air pollution. By religious proscription, Seventh-day Adventists neither use tobacco products nor drink alcoholic beverages, but do experience widely differing levels of air pollution exposure. To be included in the study, individuals must have met the following criteria;

- \* Twenty-five years or older at the time of completing the Adventist Health Study questionnaire in 1974.
- \* Member of the Seventh-day Adventist church at the time of enrollment in the Adventist

Health Study.

\* Non-Hispanic white (although individuals of all races completed questionnaires, only non-Hispanic whites were followed for cancer and heart disease surveillance).

\* Lived 10 years or longer within five miles of their present residence.

\* Resided in one of three metropolitan areas - San Francisco, Los Angeles and eastward (South Coast Air Basin), or San Diego, or be included in a random sample of 862 individuals residing in the rest of California.

Individuals meeting these criteria were mailed a baseline questionnaire which ascertained their residence history by month and zip code since 1960 as well as lifestyle habits pertinent to relative air pollution exposure such as work location, hours driving on crowded freeways, percent of time indoors/outdoors, etc. They also completed the National Heart, Lung, and Blood Institute (NHLBI) respiratory symptoms questionnaire which was used to ascertain self-reported symptoms of chronic respiratory disease. In addition, detailed smoking histories were obtained as well as histories of ever having lived or worked with a smoker and the duration of these exposures. The response fraction to the baseline questionnaire was 87%. A wide range of other lifestyle data (such as demographic and dietary information) were already available on these individuals as part of the Adventist Health Study database.

#### Cancer Monitoring Program.

Incidence: A surveillance system consisted of annual mailings to every member of the cohort between April 1, 1977 and December 31, 1982 requesting information on any hospitalization in the previous 12-month period of follow-up. If a hospitalization was

reported, the name and address of the appropriate hospital was recorded and permission to review the resulting medical record was obtained. Adventist Health Study personnel reviewed all medical records for a diagnosis of cancer or cardiovascular disease. Pertinent portions of the medical records were microfilmed to allow a confirmation of the diagnosis by senior medical personnel. Follow-up in this fashion was complete for 99% of the cohort. Computerized record linkage was conducted with those areas of the state of California with population-based tumor registries (The Cancer Surveillance Program in Los Angeles County and the Resource for Cancer Epidemiology in the San Francisco Bay area) (8).

**Mortality:** Three mechanisms were utilized to monitor mortality in the study population. These included (1) computerized record linkage with the California death certificate file (2) computerized record linkage with the National Death Index and (3) manual linkage with SDA church records. The above three mechanisms identified deaths in the study population during the follow-up period (1977-1986).

### Statistical Methods

Adjusted relative risks (ratios of incidence rates) are presented for average annual exposures to TSP and OZ exceeding cutpoints versus lower exposures. The relative risks have been adjusted for relevant covariates, including age, sex, and past smoking history.

Mantel-Haenszel analyses were performed for each outcome before the more sophisticated analyses with proportional hazards regression models. These analyses categorize continuous variables and thus avoid any assumptions of linear or additive

effects. Their disadvantages are the loss of statistical power due to this categorization and their inability to adjust for more than a few covariates (two covariates, with the sample size of the present study). The results of the Mantel-Haenszel analyses should not be considered conclusive, but should be used only as a check on the multivariate models.

The Mantel-Haenszel analyses were age-adjusted using the strata 25-44 years, 45-64 years, 65-79 years, and 80 years and older. Cumulative annual average concentrations and their annual average exceedance frequencies above several thresholds were used as indices for long-term ambient concentrations of TSP and O<sub>3</sub>. Two cutpoints for each index of exposure were determined from the index's cumulative distributions for the subcohorts residing inside and outside the SCAB. There was not much overlap between the distributions of the generally lower ambient concentrations outside the SCAB and ambient concentrations inside the SCAB. The lower of the two cutpoints was the 90th percentile of ambient concentrations outside the SCAB, and the higher cutpoint was the median of all higher ambient concentrations.

Cox proportional hazards regression models (9) for the cancer incidence and mortality outcomes which controlled for several covariates were fitted by the BMDP2L stepwise procedure (10). Cumulative ambient concentrations of TSP and O<sub>3</sub> were represented by annual average concentrations and annual average exceedance frequencies above thresholds for two time periods (1/66-3/77 and 1/73-3/77). The second later time period was allowed as an alternative for the longer time period in the models as it was felt that ambient pollutant monitoring was more representative of that

experienced in the locations of study participants during this later period due to an increased number of monitoring stations. Since all study participants had lived in their 1977 neighborhood for at least 10 years, it was felt that the later time period might provide a better ranking of the relative ambient concentrations experienced by study subjects for the longer time period. Cumulative ambient concentrations for the two time periods were allowed to compete for entry in the stepwise selection process used for original model formulation. Separate models were fitted for annual average concentrations and for exceedance frequencies above each threshold. Time-dependent Cox regression and analyses were also performed using the average pollutant exposures between 1/73 and the time of risk set as the exposure variables.

Models involving ambient concentrations of TSP and OZ were fitted separately. Models were first fit for TSP using exceedance frequencies for the threshold of 200 micrograms per cubic meter (TSP200) and ozone using exceedance frequencies for the threshold of 10 parts per hundred million (OZ10). For each pollutant the variables selected for these thresholds were then used for the other thresholds as well as mean concentration. The primary candidate independent variables -- total years of smoking, gender, and education -- were forced into each model. Age was not among the covariates because age, instead of time on study, was used as the time variable in the models as recommended by Breslow (11). The secondary candidate independent variables considered for entry into the models were: years lived with a smoker, years worked with a smoker, and past or present employment in an occupation having high exposures to airborne contaminants. A list of the occupations in which study

participants had high exposures is given in Euler et al (3).

The pollutant exposure variable or variables and the secondary candidate variables competed for entry by the stepwise selection procedure. An F to remove of 0.15 and an F to enter of 0.10 were used to terminate the stepwise procedure. The final models chosen required an F to enter of 0.05 or less.

Interactions between TSP or OZ and the other covariates were assessed by including first-order cross-product terms in the model, then removing them and noting the change in the log-likelihood.

## **RESULTS**

Three different disease outcomes were analyzed in this analysis: All malignant neoplasms for males, all malignant neoplasms for females, and respiratory cancers in all subjects. All malignant neoplasms in males and females were analyzed separately because some cancer sites are sex-specific.

The distributions of the air pollution variables and relevant covariates (e.g. past history of smoking, education) are shown in Table 1. Approximately 62% of the study population resided within the South Coast Air Basin. Between the start of follow-up on April 1, 1977 and the end of incidence follow-up on December 31, 1982, there were 290 newly diagnosed cancers (ICDO 140-200) detected in the population. Only seventeen respiratory cancers were diagnosed. During the mortality follow-up period, 1977-1986, there were 180 cancer deaths.

### **CANCER INCIDENCE**

The results of the stepwise regressions indicated that exceedance frequencies



during the time period 1/73-3/77 were most closely associated with cancer risk between 1977 and 1982. For this reason, average annual exceedance frequencies during this time period were used in the regression analyses. However, all results were checked by using exceedance frequencies for the longer time period, 1966-1977, and only minor differences in the results were noted. The Cox proportional hazards regression models which were fitted each included exceedance frequency variables for a threshold of TSP or OZ, as well as covariates including gender, education, total years of past smoking and past or present employment in occupations involving exposure to airborne contaminants. (Occupational exposures were included for males only, since females lacked sufficient exposure). The passive smoking variables did not contribute sufficiently to the fit of the model to be included.

The result of the multivariate analysis of TSP200 is shown in Table 2. For 1,000 hours per year in excess of this threshold, the relative risk for all malignant neoplasms among females is 1.37, which is statistically significant ( $p < 0.05$ ). For respiratory cancers (Table 3) the relative risk for 1,000 hours in excess is 1.72; however, this risk is not statistically significant.

Relative risk contour plots for the associations between all malignant neoplasms in females and TSP exposures are shown in Figure 1. The relative risks for all thresholds except TSP60 are statistically significant. Figure 2 displays the "dose-response" type curves for the various thresholds of TSP.

The results of the multivariate TSP analyses for the other thresholds and for mean concentration are presented in Table 4. Separate Cox regressions were used

for each threshold with the same covariates as for TSP200. Statistically significant increases in cancer risk are seen among females for all thresholds except for TSP60. The magnitude of the increased risk for females is approximately 40-60%. Two-fold increases in risk are observed for the respiratory cancers, although these risks are not statistically significant. Again, there is no relationship between TSP ambient concentrations and cancer incidence in the males.

The results of the Cox regressions relating respiratory cancer incidence and OZ ambient concentrations are presented in Table 5. For 500 hours in excess of OZ10, the relative risk for respiratory cancer is 2.25, which is of borderline statistical significance. Statistical significance was not achieved for any of the other thresholds or for mean concentration. The results of the Cox proportional hazards regression analysis were very similar to the results which were obtained in the Mantel-Haenszel stratified analysis. In the stratified analysis only age and sex were controlled.

#### **MULTI-POLLUTANT ANALYSIS**

We evaluated the relative contributions of TSP and OZ to cancer risk by comparing the contributions of the TSP and OZ thresholds most strongly associated with risk in both the Mantel-Haenszel and the Cox regression analyses - 200 mcg/m<sup>3</sup> for TSP and 10 pphm for OZ. Exceedance frequencies for these thresholds were allowed to compete for entry into a stepwise Cox regression procedure into which terms for gender, education and total years of past smoking had already been entered. For respiratory cancer OZ10 entered the model with a p to enter value which was of borderline statistical significance ( $p = 0.055$ ), and TSP200 did not enter. For all

malignant neoplasms among females, TSP200 entered the model ( $p$  to enter = 0.038), but OZ10 did not.

### **CANCER MORTALITY**

The same Cox proportional hazards regression models were fit to the mortality data as were fit to the incidence data. Covariates included total years of smoking and education (as a surrogate measure of social class). Past or present experience in an occupation with high levels of airborne contaminants was also included for the males. Increasing average annual hours of exposure to TSP above the various thresholds were associated with increased risk of malignant neoplasms in males but not for females. Respiratory cancer risks were elevated but were not statistically significant. The increased risks for the males for the different thresholds of TSP were of borderline statistical significance ( $p = 0.04-0.06$ ).

For OZ, there were no statistically significantly increased risks of malignant neoplasms in either males or females. For the respiratory cancers, only one threshold level approached statistical significance (OZ20;  $p = 0.07$ ).

### **DISCUSSION**

The associations between long term ambient concentrations of TSP and OZ and cancer incidence and mortality rates in this study were observed in a unique population of currently non-smoking California Seventh-day Adventists. The lower cancer mortality rates of Adventists (12) may be partially due to their lifestyles; they do not consume tobacco or alcohol, and are vegetarians. Moreover, to ensure residential stability for a prolonged time period, participants in this study must have lived within five miles of

their 1977 residence for at least ten years. Cancer incidence reporting in this population between 1977 and 1982 has been shown to be nearly 100% complete (13) and loss to follow-up has been minimal.

In this population, increasing long-term ambient concentrations of TSP was associated with increased risk of all cancers combined among females, and the largest increases in risk estimates occurred among the smoking-related respiratory cancers (Larynx, lung, pleura). Risk of all newly diagnosed cancers in females increased with increasing threshold levels of TSP and were statistically significant for all thresholds of 100 mcg/m<sup>3</sup> or more, although this increase in risk was not observed among males. For females, this excess risk was approximately two-fold in the age-adjusted Mantel-Haenszel analysis and of similar magnitude in the multivariate Cox analysis. For the smoking-related respiratory cancers, the corresponding risk increases were threefold and greater.

For OZ, there were statistically significant increases in respiratory cancer risk and risk of all malignant neoplasms in females was elevated, though not significantly so.

The analysis of cancer mortality showed somewhat stronger (though non-significant) results in the males than females, however. These results were observed after an increase in the follow-up period by an additional four years for the mortality analysis.

An explanation of the higher cancer incidence risk in females associated with TSP is not immediately apparent. Much smaller percentages of the females had been exposed to tobacco smoke and occupational fumes and dust. Only 14% of the females

had a history of past smoking, compared to 36% of the males. Moreover, only 5% of the females had smoked for ten years or more, whereas 17% of the males had smoked that long. In addition, only 1% of the females reported having ever worked in a hazardous occupation where exposure to fumes and dust was common (compared to 14% of the males). There is some evidence that the increased risk of lung cancer associated with urban living is more apparent in non-smokers than smokers (1, 14 and 15). This is consistent with females' stronger relationship between ambient concentrations of TSP and cancer incidence in this study.

Particulate matter in ambient air is known to contain substances which exhibit carcinogenic activity in experimental systems (16). The polycyclic aromatic hydrocarbons have received the most attention; several are known to be carcinogens in both animals and humans (17). A direct relationship between increasing exposure to TSP and increasing cancer incidence and mortality rates would therefore be expected. Earlier work has suggested a relationship between ambient sulfates and particulates in relation to total mortality among 117 S.M.S.A. in the U.S. in 1960 (18). One of the criteria proposed by Sir Austin B. Hill (19) for invoking a causal relationship between two variables is the presence of a biologic gradient. Such gradients are evident in our data.

Although the majority of studies attempting to evaluate the air pollution-cancer relationship have focused on lung cancer (e.g. 20), several studies have investigated relationships with cancer at all sites and non-respiratory tract cancers. For example, Winkelstein and Kantor found that both stomach and prostate cancer mortality rates

were higher in the area of Buffalo, New York with higher TSP pollution than in the less polluted areas (21, 22). Other investigators noted significantly higher mortality rates for cancers of the stomach, esophagus, and bladder in more highly polluted areas of Nashville, Tennessee than in less polluted areas (23). In the present study, large increases in risk of respiratory cancer were found to be associated with elevated TSP ambient concentrations, yet increased risks for all malignant neoplasms were also observed, especially in females. These increased risks suggest that high ambient levels of TSP may have both local and systemic effects on cancer induction. Tobacco smoke exhibits similar effects. It greatly enhances the risk of tumors arising in the bronchial lining of the lung, which has a direct, intimate contact with the smoke, but also enhances the risk of cancers in the pancreas and bladder, which are exposed to carcinogenic metabolites of various tobacco constituents (24).

Only one case-control study of air pollution and lung cancer has been reported to date (25). In that study of white males, cases (n = 417) and controls (n = 752) were selected from residents of areas of high, medium, or low TSP levels (the maximum level was 200 mcg/m<sup>3</sup>). The authors reported a non-significant odds ratio of 1.26 for residence in the high pollution area. Despite these findings, the authors pointed out that there was increased lung cancer risk from smoking and occupational exposure if there was also long-term exposure to air pollution.

This study has several strengths which have generally been lacking in previous studies of relationships between concentrations of ambient air pollutants and risks of cancer. The study was prospective in nature and was based on a population of

currently non-smoking Seventh-day Adventists who were geographically stable for a period of at least ten years prior to the beginning of follow-up for cancer incidence and mortality. These characteristics of the study population would remove confounding due to current smoking and limit any bias due to migration patterns during the follow-up period (either out-migration to escape the relatively polluted areas under study or in-migration). It is possible however, that individuals most sensitive to air pollution move out of higher pollution areas before 10 years has elapsed and thus would fail to be included in our study population. If this is the case, the net result would be to bias our results towards the null. All incident cancers were diagnosed beginning in 1977, whereas ambient air pollution concentrations were ascertained beginning in 1966.

The majority of prior studies have relied upon inexact measures of ambient concentration levels for study subjects. These have attempted to characterize individual experience by using census tract level measurements (2) as well as county and even state wide levels of measurements. The dangers of inferring exposure-disease relationships at the individual level by using aggregate exposure data are well known. We have the same problem to a degree.

The analysis of respiratory cancer was plagued by the small number of events during the six year period of follow-up ( $n = 17$ ). We plan to extend the mortality follow-up for an additional four years and to conduct a nested case-control study within the cohort with a larger number of respiratory cancer cases and an appropriate reference group.

Another limitation of the present study is that ambient concentrations of TSP and

OZ were evaluated but indoor concentrations were not. There are no known sources of ozone indoors and the indoor/outdoor concentration ratio for ozone has been estimated to range from 0.1 to 0.7 (26). It is, therefore, likely that our population's actual exposures to ozone are considerably smaller than our estimates of ambient concentrations. Therefore, our findings of increased risk are most likely conservative with respect to magnitude of effect.

Efforts are currently underway to apply adjustment factors to ambient concentrations using housing characteristics and estimates of percent of time spent outdoors for surviving members of the cohort. These efforts may enable crude estimates of exposure to ambient pollutants to be formed. It will not be possible, however, to form such exposure estimates for study participants who are deceased or lost to follow-up, nor to retrospectively apply such estimates to residence histories prior to 1977 when the study began. Thus for studying associations with cancer incidence and mortality for which long latency periods are expected, this study is limited to ambient concentrations. The uncontrolled variability thus introduced would bias hypotheses tests towards the null which may explain lack of statistical significance for ozone effects. (27)

As a further check on our results we restricted interpolations to be within the A or B quality range, considered representative by EPA and we ran the final regression models using TSP<sub>200</sub> and TSP mean concentration as the exposure variables. For TSP this reduced the number of individuals available for analysis by approximately one-half. The regression coefficients were essentially unchanged for the cancer outcomes,



after applying these restriction criteria.

Relating health effects directly to ambient community concentrations is however relevant, since air quality standards are regulated by ambient concentrations.

The same problems apply to TSP, although one of the primary sources of indoor TSP is cigarette smoking, which has been taken into account in the present analysis. However, the most recent work suggests that TSP may not be the best measure of toxic particulates suspected of causing adverse health effects. The fine particulate fraction of TSP (<2.5 microns in aerodynamic diameter) is currently considered the most hazardous. Present plans call for estimating fine particulate exposures as well as exposures to  $\text{NO}_2$ ,  $\text{SO}_2$ , and  $\text{SO}_4$  in our ongoing prospective study.

Finally, there are problems in statistically separating the effects of air pollutants whose concentrations in the ambient air are highly correlated. Human chamber studies may be able to untangle this multi-collinearity, but such studies are not feasible for free-living human populations.

In summary, cancer incidence and mortality risk were clearly associated with increasing exposure to ambient TSP levels in this unique population of non-smokers. Cancer incidence appeared to be more closely associated with TSP in the females.

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**TABLE 1**  
**FREQUENCY DISTRIBUTIONS OF PAST AND PASSIVE SMOKING**  
**VARIABLES, AIR POLLUTION VARIABLES AND COVARIATES IN**  
**THE AHSMOG INCIDENCE COHORT**

VARIABLE	FEMALES N = 4063		MALES N = 2277	
	No.	(%)	No.	(%)
<b>History of Smoking</b>				
Never	3504	(86)	1450	(64)
Past Only	559	(14)	827	(36)
<b>Pack Years of Cigarette Smoking</b>				
None	3475	(86)	1484	(65)
< 10 pack years	335	(08)	339	(15)
≥ 10 pack years	196	(05)	390	(17)
Unknown	57	(01)	64	(03)
<b>Total Years of Smoking</b>				
Never	3519	(87)	1507	(66)
1-9 years	292	(07)	312	(14)
≥ 10 years	246	(06)	429	(19)
Unknown	6	(01)	30	(01)
<b>Age (4-1-77)</b>				
25-44 years	698	(17)	358	(16)
45-64 years	1863	(46)	1170	(51)
65-80 years	1149	(28)	599	(26)
> 80 years	353	(09)	150	(07)
<b>Education</b>				
Some high school	868	(21)	417	(18)
High school grad	695	(17)	249	(11)
Some college	1715	(42)	743	(33)
College grad	760	(19)	856	(38)
Unknown	25	(01)	12	(01)
<b>Occupational Air Pollution</b>				
No	4026	(99)	1964	(86)
Yes	37	(01)	313	(14)
<b>Years lived with a smoker</b>				
Never	2119	(52)	1508	(66)
1-9 years	403	(10)	236	(10)
≥ 10 years	1541	(38)	533	(23)
Unknown	-0-	(0)	-0-	(0)

**TABLE 1 (CONT'D)**  
**FREQUENCY DISTRIBUTION OF PAST AND PASSIVE SMOKING**  
**VARIABLES, AIR POLLUTION VARIABLES AND COVARIATES**  
**IN THE AHSMOG INCIDENCE COHORT**

VARIABLE	FEMALES N = 4063		MALES N = 2277	
<b>Years worked with a smoker</b>				
Never	2512	(62)	1183	(52)
1-9 years	815	(20)	392	(17)
≥ 10 years	736	(18)	702	(31)
Unknown	-0-	(0)	-0-	(0)
<b>*South Coast Air Basin</b>				
Outside	1305	(32)	738	(32)
Inside	2533	(62)	1381	(61)
Mixed	225	(06)	158	(07)
<b>TSP60 Average Annual Exposure**</b>				
Unknown	141	(03)	63	(03)
≤ 6000 hrs/yr.	1276	(31)	710	(31)
6001-7500 hrs/yr.	1563	(38)	866	(38)
> 7500 hrs/yr.	1083	(27)	638	(28)
<b>TSP100</b>				
Unknown	141	(03)	63	(03)
≤ 3000 hrs/yr.	1455	(36)	804	(35)
3001-5000 hrs/yr.	1473	(36)	815	(36)
> 5000 hrs/yr.	994	(24)	595	(26)
<b>TSP150</b>				
Unknown	141	(03)	63	(03)
≤ 750 hrs/yr.	1442	(35)	795	(35)
751-2000 hrs/yr.	1406	(35)	778	(34)
> 2000 hrs/yr.	1074	(26)	641	(28)
<b>TSP200</b>				
Unknown	141	(03)	63	(03)
< 125 hrs/yr.	1287	(32)	709	(31)
126-1000 hrs/yr.	1814	(45)	987	(43)
> 1000 hrs/yr.	821	(20)	518	(23)
<b>TSP Mean Concentration</b>				
< 92.41 mcg/m <sup>3</sup>	1361	(35)	758	(34)
92.41-114.37 mcg/m <sup>3</sup>	1260	(32)	696	(31)
> 114.37 mcg/m <sup>3</sup>	1268	(33)	760	(34)

\* Residence inside or outside the South Coast Air Basin, 1973-1977

\*\* Average annual hours of exposure to indicated threshold of total suspended particulates (e.g. 60 or more micrograms per cubic meter) 1973 to earliest of 1) date of censoring, 2) date of death or 3) Dec. 31, 1982.

**TABLE 1 (CONT'D)**  
**FREQUENCY DISTRIBUTION OF PAST AND PASSIVE SMOKING**  
**VARIABLES, AIR POLLUTION VARIABLES AND COVARIATES**  
**IN THE AHSMOG INCIDENCE COHORT**

VARIABLE	FEMALES N = 4063		MALES N = 2277	
	No.	(%)	No.	(%)
<b>OZ10</b>				
Unknown	37	(01)	0	(0)
< 60 hrs/yr.	1442	(35)	774	(34)
60-600 hrs/yr.	1426	(36)	865	(38)
> 600 hrs/yr.	1138	(28)	638	(28)
<b>OZ12</b>				
Unknown	37	(01)	0	(0)
< 25 hrs/yr.	1381	(34)	751	(33)
25-400 hrs/yr.	1503	(37)	706	(31)
> 400 hrs/yr.	2925	(28)	820	(36)
<b>OZ15</b>				
Unknown	37	(01)	0	(0)
< 8 Hrs/yr.	1463	(36)	797	(35)
8-200 Hrs/yr.	1463	(36)	842	(37)
> 200 Hrs/yr.	1097	(27)	638	(28)
<b>OZ20</b>				
Unknown	37	(01)	0	(0)
< 1 Hr/yr.	1463	(36)	797	(35)
1-50 Hrs/yr.	1300	(32)	774	(34)
> 50 Hrs/yr.	1260	(31)	706	(31)
<b>OZ25</b>				
Unknown	37	(01)	0	(0)
0 Hrs/yr.	1463	(36)	797	(35)
> 0-10 Hrs/yr.	1016	(25)	569	(25)
> 10 Hrs/yr.	1544	(38)	911	(40)
<b>OZ Mean Concentration</b>				
< 2.6 pphm	1779	(46)	1000	(46)
2.6-3.1 pphm	1138	(29)	686	(31)
> 3.1 pphm	952	(25)	503	(23)

\* Residence inside or outside the South Coast Air Basin, 1973-1977

\*\* Average annual hours of exposure to indicated threshold of total suspended particulates (e.g. 60 or more micrograms per cubic meter) 1973 to earliest of 1) date of censoring, 2) date of death or 3) Dec. 31, 1982.



**TABLE 2**  
**COX PROPORTIONAL HAZARDS REGRESSION FOR ALL MALIGNANT NEOPLASMS**  
**AMONG FEMALES, 1977-82, WITH HOURS AVERAGE ANNUAL CONCENTRATION**  
**IN EXCESS OF 200 MCG/M<sup>3</sup> OF TOTAL SUSPENDED PARTICULATES AS THE**  
**AIR POLLUTION EXPOSURE VARIABLE**

(N = 4063, Cases = 175)

<u>Variable</u>	<u>Regression Coefficient</u>	<u>Increment<sup>(2)</sup></u>	<u>Relative Risk<sup>(3)</sup></u>	<u>95% C.I. for Relative Risk</u>
TSP (Hrs. in Excess of 200 mcg/m <sup>3</sup> ) <sup>(1)</sup>	0.0003174*	1000 hr/yr.	1.37	1.05, 1.80
Total Years Smoked	0.0223	10 years	1.25	0.98, 1.59
Education	0.0424	4 years	1.18	0.94, 1.50

(1) Average annual hours in excess of 200 mcg/m<sup>3</sup> 1973-1977.

(2) Increment for computations of relative risk.

(3) Relative risk of increase in exposure of one increment, holding other variables in model constant.

\* p < 0.05

**TABLE 3**  
**COX PROPORTIONAL HAZARDS REGRESSION FOR RESPIRATORY CANCER,**  
**1977-82, WITH HOURS AVERAGE ANNUAL CONCENTRATION IN EXCESS**  
**OF 200 MCG/M<sup>3</sup> OF TOTAL SUSPENDED PARTICULATES AS THE AIR**  
**POLLUTION EXPOSURE VARIABLE**

(N = 6301, Cases = 17)

<u>Variable</u>	<u>Regression Coefficient</u>	<u>Increment<sup>(2)</sup></u>	<u>Relative Risk<sup>(3)</sup></u>	<u>95% C.I. for Relative Risk</u>
TSP (Hrs. in Excess of 200 mcg/m <sup>3</sup> ) <sup>(1)</sup>	0.0005406	1000 hr/yr.	1.72	0.81, 3.65
Gender	0.9960	(F,M)	2.71	0.92, 7.98
Total Years Smoked	0.0384*	10 years	1.47	1.01, 2.14
Education	0.0246	4 years	1.10	0.60, 2.02

(1) Average annual hours in excess of 200 mcg/m<sup>3</sup> 1973-1977.

(2) Increment for computations of relative risk.

(3) Relative risk of increase in exposure of one increment, holding other variables in model constant.

\* p < 0.05

**TABLE 4**  
**ESTIMATES OF CANCER INCIDENCE (1977-82) RELATIVE RISKS FROM COX PROPORTIONAL HAZARDS REGRESSIONS FOR INCREMENTAL INCREASES OF EXPOSURE + ABOVE VARIOUS THRESHOLD LEVELS OF TOTAL SUSPENDED PARTICULATES AND FOR MEAN CONCENTRATION OF TOTAL SUSPENDED PARTICULATES**

Threshold Level	% Person-years in Excess of Increment	Increment <sup>(1)</sup> Size	All Malignant Neoplasms		Smoking Related Respiratory Cancers (N = 17)
			MALES (N = 108)	FEMALES (N = 175)	
60 mcg/m <sup>3</sup>	99.7	1000 Hrs/yr	1.04	1.05	1.21
	88.1	3500	1.13	1.18	1.96
	77.50	5000	1.19	1.27	2.62
100 mcg/m <sup>3</sup>	83.0	1000 Hrs/yr	1.02	1.10*	1.21
	43.0	2500	1.04	1.27*	1.60
	24.6	5000	1.08	1.61*	2.55
150 mcg/m <sup>3</sup>	67.4	500 Hrs/yr	1.00	1.09 <sup>x</sup>	1.15
	54.7	1000	1.00	1.18 <sup>x</sup>	1.33
	23.0	2500	0.99	1.52 <sup>x</sup>	2.04
200 mcg/m <sup>3</sup>	48.8	250 Hrs/yr	0.99	1.08 <sup>o</sup>	1.14
	31.5	500	0.98	1.17 <sup>o</sup>	1.31
	26.9	750	0.97	1.27 <sup>o</sup>	1.50
Mean Concentration	21.3	1000	0.96	1.37 <sup>o</sup>	1.72
	98.3	50 mcg/m <sup>3</sup>	1.03	1.26	1.73
	60.7	100 mcg/m <sup>3</sup>	1.06	1.60	2.98

(1) Increment for computations of relative risk.

\* p = 0.04

x p = 0.01

o p < 0.02

+ Average Annual Concentration 1773 to 3177

**TABLE 5**  
**COX PROPORTIONAL HAZARDS REGRESSION FOR RESPIRATORY CANCER,**  
**1977-82, WITH ANNUAL AVERAGE HOURS IN EXCESS OF 10 PPHM**  
**OZONE AS THE AIR POLLUTION EXPOSURE VARIABLE**

(n = 6301, Cases = 17)

<u>Variable</u>	<u>Coefficient</u>	<u>Increment<sup>(2)</sup></u>	<u>Relative Risk<sup>(3)</sup></u>	<u>95% C.I. for Relative Risk</u>
Oxidants (Hrs. in Excess of 10 pphm) <sup>(1)</sup>	0.0016256 <sup>+</sup>	500 hrs/yr.	2.25	0.96, 5.31
Gender	1.2858*	(F,M)	3.62	1.16, 11.25
Total Years Smoked	0.0333	10 years	1.40	0.93, 2.09
Education	0.0226	4 years	1.09	0.59, 2.03

(1) Average annual hours in excess of 10 pphm, 1973-1977.

(2) Increment for computations of relative risk.

(3) Relative risk of increase in exposure of one increment, holding other variables in model constant.

\* p < 0.05

+ p = 0.055

Days

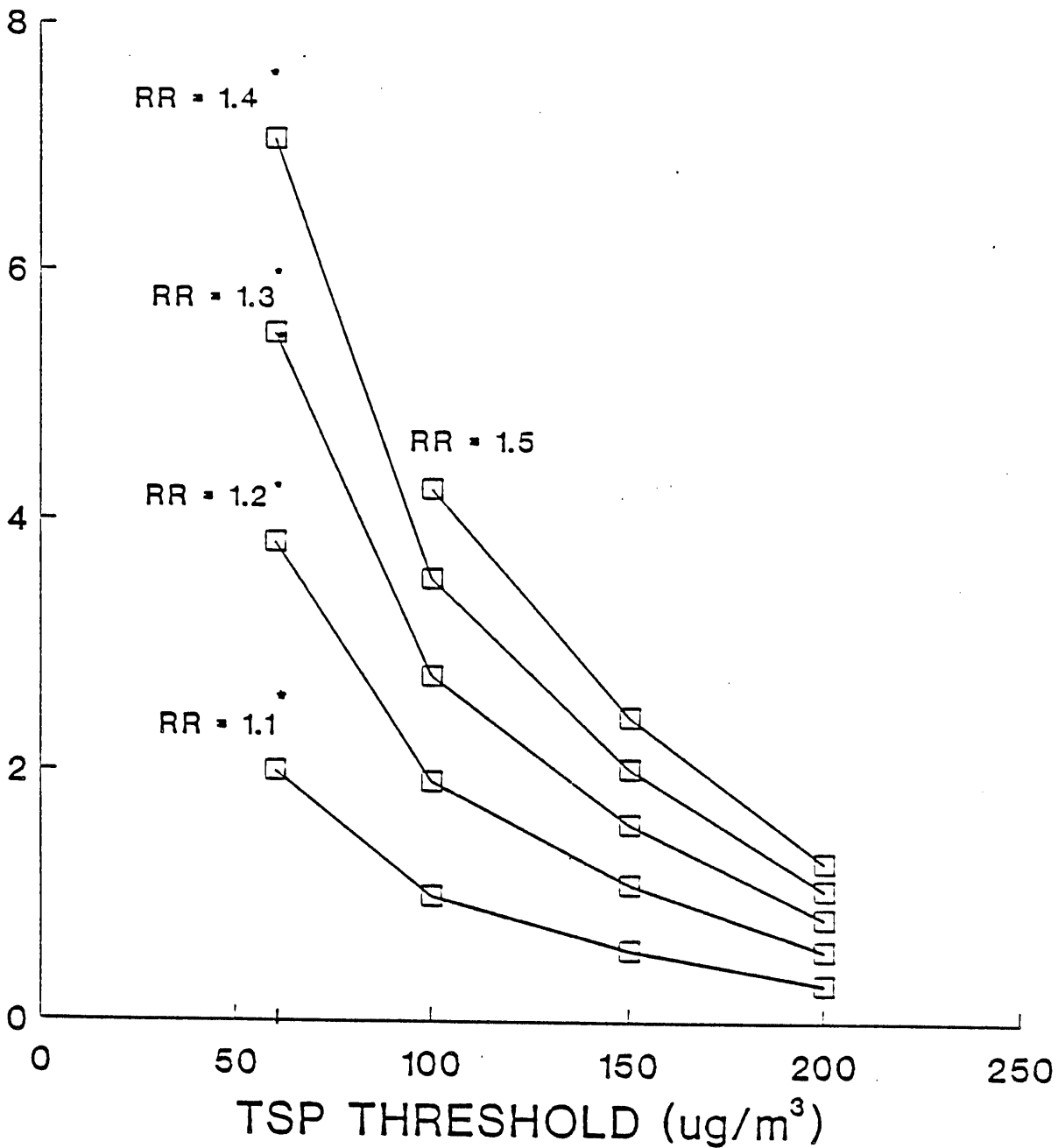
Hours<sup>\*\*\*</sup> x 1000

(333)

(250)

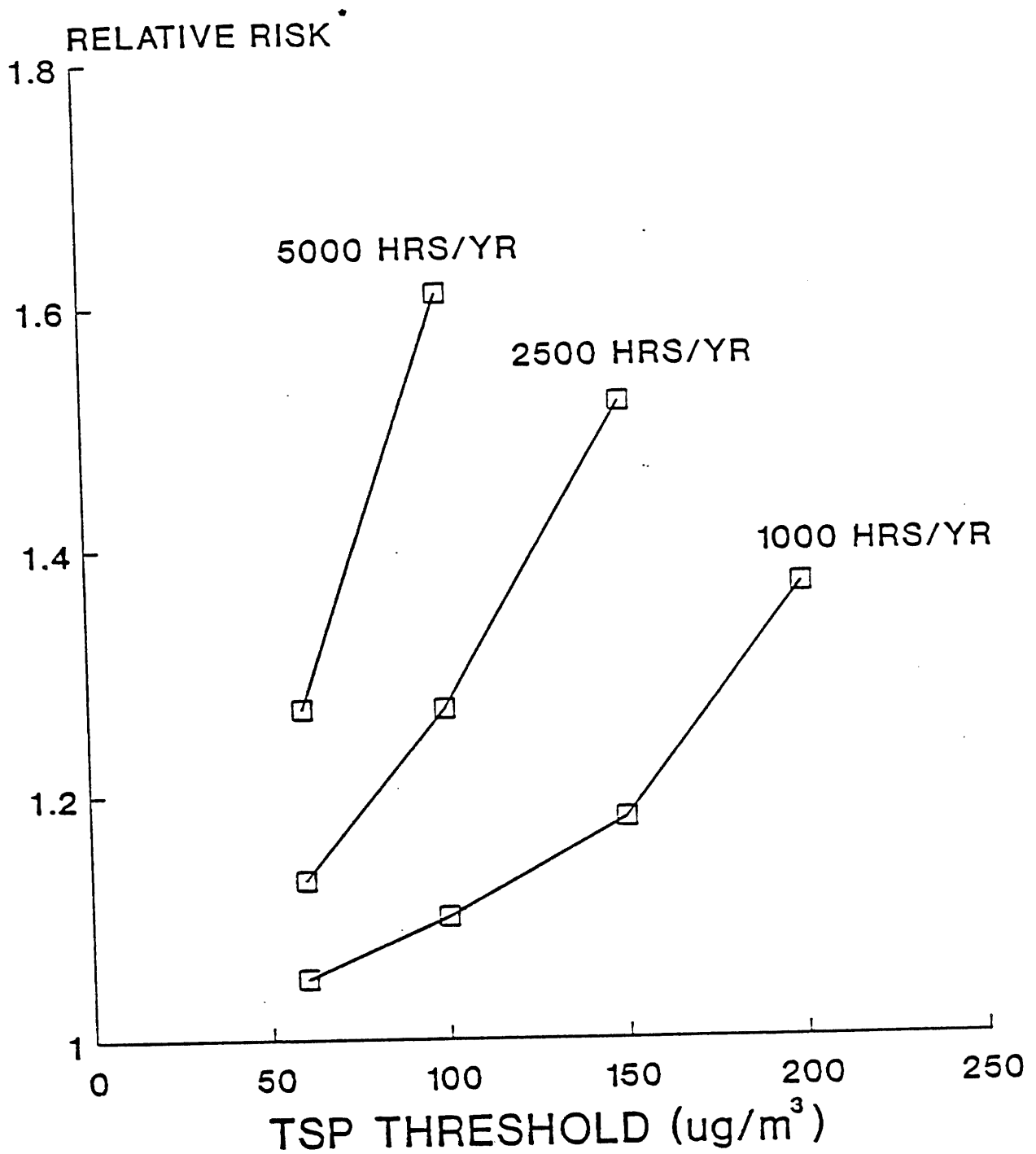
(167)

(83)



\* RISKS FOR LOWEST THRESHOLD NOT STATISTICALLY SIGNIFICANT.  
- AVERAGE ANNUAL HOURS 1973-1977.

Fig.1. Relative Risk Contour Plots for All Malignant Neoplasms (Female) Associated with TSP.



• RISKS FOR TSP60 NOT STATISTICALLY SIGNIFICANT

Fig.2. Relative Risk of All Malignant Neoplasms Among Females for Differing Annual Average Hours (1973-1977) in Excess of 60, 100, 150 and 200  $\text{mcg}/\text{m}^3$  of Total Suspended Particulates.

**LONG TERM AMBIENT CONCENTRATIONS OF TOTAL SUSPENDED  
PARTICULATES AND OZONE AND INCIDENCE OF RESPIRATORY SYMPTOMS  
IN A NON-SMOKING POPULATION**

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## ABSTRACT

Seventh-day Adventist non-smokers who had resided since 1966 within five miles of their 1977 residence (N = 3914), completed the National Heart, Lung, and Blood Institute (NHLBI) respiratory symptoms questionnaire in 1977 and again in 1987. For each participant cumulative ambient concentrations of total suspended particulates (TSP) and ozone in excess of several thresholds were estimated month by month, by interpolating ambient concentrations from state air monitoring stations to their residential and workplace zip codes for the month. Relationships between ambient concentrations of these air pollutants were evaluated in regard to several respiratory disease outcomes. Multivariate analyses which adjusted for past and passive smoking and occupational exposures indicated statistically significant ( $p < 0.05$ ) elevated relative risks for the incidence of asthma, definite symptoms of airway obstructive disease (AOD), and chronic bronchitis in relation to increased average annual hours of TSP above a number of thresholds. These elevated relative risks were observed for mean concentration of these pollutants as well. There were no significantly elevated risks associated with excesses of any threshold of ozone. Mean concentration of ozone, however, was significantly associated with increased asthma incidence. Increased severity of respiratory symptoms was significantly associated with a number of thresholds of both TSP and ozone. These results are discussed within the context of standards setting for TSP and ozone.

## INTRODUCTION

Seventh-day Adventists (SDA) provide a unique population in which to evaluate health effects of ambient air pollutants. By church proscription SDAs do not use tobacco so that confounding by current smoking is not an issue in evaluating health effects of air pollutants. In California, however, SDAs live in areas differing widely in concentrations of ambient air pollutants and thus variability in exposure enhances power to detect alteration in risk.

Previous papers (1,2,3) on this study termed the AHSMOG study have reported associations between prevalence of definite symptoms of airway obstructive disease (AOD) and long-term ambient concentrations of total suspended particulates (TSP), total oxidants, nitrogen dioxide ( $\text{NO}_2$ ), and sulfur dioxide ( $\text{SO}_2$ ). In those papers the average annual exceedance frequency for TSP60 was not significantly related with prevalence of AOD although the exceedance frequencies for TSP100, TSP150 and TSP200 were. Moreover, a highly statistically significant association between prevalence of definite AOD symptoms and the average annual exceedance frequencies of ozone (OZ) 10, OZ15 and OZ20 was noted in that study.

The previous studies, however, were limited to the analysis of cross-sectional data and the limitations of prevalence studies were addressed (2). Incidence data for a ten year period are now available and are reported here. In this report we present associations between long-term cumulative ambient concentrations of total suspended particulates and ozone and the following adverse health effects: (1) the cumulative incidence of definite symptoms of AOD, chronic bronchitis and asthma, 1977-1987 and

(2) the change in severity of these symptom complexes, 1977-1987.

## METHODS

### Enrollment and Follow-up of Cohort

All participants in the current study had completed a detailed lifestyle questionnaire in 1976 as part of the Adventist Health Study, an N.I.H. funded study of lifestyle and cancer in SDAs (REF). This questionnaire ascertained demographic and dietary information as well as lifestyle factors thought to be related to cancer and heart disease incidence. In April of 1977, a subset (N = 7,445) of the subjects who completed the AHS questionnaire completed the National Heart, Lung, and Blood Institute (NHLBI) respiratory symptoms questionnaire as well which was used to ascertain self-reported symptoms of chronic respiratory disease. In addition, detailed smoking histories were obtained and histories of ever having lived or worked with a smoker and the duration of these exposures. Residence and work location history was ascertained by month and zip code since 1966. The questionnaire also ascertained lifestyle factors pertinent to relative air pollution exposure such as occupational exposures, hours spent driving on crowded freeways, percent of time spent indoors/outdoors, etc. The response fraction to the 1977 questionnaire was 87%. Of the 7,445 individuals who completed the April, 1977 questionnaire, 6,340 were followed prospectively for chronic disease incidence and mortality. To be included in the prospective cohort, individuals must have met the following criteria:

- \* Twenty-five years or older at the time of completing the Adventist Health Questionnaire in 1974;

\* Baptized member of the Seventh-day Adventist church at the time of enrollment in the Adventist Health Study;

\* Non-hispanic white (although individuals of all races completed questionnaires, only non-hispanic whites were followed in the cancer and heart disease surveillance project);

\* Living ten years or longer within five miles of the present residence;

\* Residing in one of three metropolitan areas - San Francisco, the South Coast Air Basin, (i.e. Los Angeles and eastward), or San Diego, or being included in a random sample of 862 individuals residing in the rest of California.

Of the 5,261 individuals who were not deceased by April of 1987, 87% returned the follow-up questionnaire. This questionnaire again ascertained the presence of respiratory symptoms, the residence and work location history since 1977, and household and lifestyle characteristics relevant to relative air pollution exposure.

#### **Definition of Health Outcomes**

Computer algorithms were used to classify individuals as having chronic bronchitis, asthma, or emphysema. These computer algorithms were based on 21 respiratory symptoms questions from the standard NHLBI questionnaire. Hodgkin (1) lists the respiratory symptoms questions which were used and gives the percentage of individuals having each symptom; they are explicitly defined by Abbey (4).

The computer algorithms classified individuals as having "definite" chronic bronchitis, "definite" emphysema, or "definite" asthma. Individuals meeting the criteria for one of these three diagnoses were classified as having "definite" airway obstructive

disease (AOD). To be classified as having "definite" chronic bronchitis, individuals must have had symptoms of cough and/or sputum production on most days, for at least three months per year, for two years or more. For a diagnosis of "definite" asthma, individuals must have been told by their physician that they had asthma, as well as having a history of wheezing. For emphysema, subjects must have been told by their physician that they had emphysema, as well as having shortness of breath when walking or exercising. Individuals not meeting the criteria for "definite" symptoms for a respiratory symptoms complex, but having some respiratory symptoms associated with that complex, were classified as "possible". In addition to a classification of "none", "possible", or "definite" for each respiratory symptoms complex, a severity score was developed for each respiratory symptoms complex as well as for overall AOD to reflect the relative severity of the symptoms. The detailed definitions of these scores are given in Abbey (4).

The computer algorithms were used to classify and score the individual's respiratory symptoms complexes as ascertained by questionnaire in 1977 and again in 1987. Since there were an insufficient number of cases of emphysema to warrant disease specific analyses for this outcome, we restricted analyses to the three outcomes - AOD, chronic bronchitis, and asthma. Cumulative incidence for each of these outcomes was defined as having definite symptoms in 1987 but not having definite symptoms in 1977.

## Statistical Models

Multiple logistic regression models were used for studying associations between cumulative incidence of definite respiratory symptoms and long-term cumulative ambient concentrations of air pollution. Individuals having definite symptoms in 1977 were excluded from analyses which used cumulative incidence as an outcome. Individuals having possible symptoms in 1977 were included in such analyses and a covariate was included to this effect. Another set of statistical analyses used change in the respiratory symptoms severity score as the outcome variable. All individuals were included in these analyses, with a positive value of change in score indicating an increase in severity of symptoms and a negative value indicating a decrease in severity of symptoms. The 1977 symptoms severity score was used as a covariate in these analyses. Multiple linear regression models were used for studying associations between change in respiratory symptoms severity score and long-term cumulative ambient concentrations of air pollutants.

Multivariate models were used in order to adjust for a number of covariates simultaneously. The candidate covariates for the multivariate models are shown in Table 1, along with their descriptive statistics for the cohort, including the mean values and maximum values of continuous variables and the percent having zero or no exposure to that variable. The mean values for age, education, TSP, and ozone are averages over the entire cohort, including possible zero values as well as non-zero values. For the other continuous variables in this table, such as years smoked in the past, the mean value is given for only those individuals who had non-zero values, i.e.

only for those who have smoked in the past.

In order to ensure adjustment for demographic characteristics, three demographic variables - gender, age, and education - were forced into all multivariate analyses. Education was used as the best surrogate in this population for socioeconomic level. As some Adventists work for the church for "missionary" wages, we felt that education was a better indicator of socioeconomic level for this population than income.

Stepwise selection procedures were used to determine a final model by selecting from among the secondary variables (all those other than the demographic factors), those variables which were most strongly and statistically significantly related to the outcome variable. These stepwise procedures were stopped when additional candidate variables entering the model failed to achieve statistical significance at the 0.05 level. For the variables which represented cumulative exposures over time, such as passive smoking and ambient air pollutants, three forms were allowed to compete with each other for entry; these forms corresponded to lifetime through 1977, exposures from 1977 through 1987, and lifetime through 1987. For total suspended particulates and ozone, "lifetime" was replaced with cumulations since 1973 which was used as a surrogate for cumulations since 1966. It was felt that interpolations since 1973 were of better quality since the number of monitoring stations greatly increased in 1973. The final models were checked by replacing cumulations since 1973 with cumulations since 1966. In no case were significant changes in results noted.

Initial stepwise regression analyses were run separately for TSP and ozone, (i.e.

they were not allowed to compete for entry into the same model). The threshold levels of 200 mcg/m<sup>3</sup> for TSP and 10 pphm for ozone (OZ10) were used for initial model determination, since they were the most significantly related to prevalence of AOD in previous analyses (5). Once a final model for TSP200 or OZ10 was determined, the model was repeated, retaining the same set of covariates (but allowing their regression coefficients to change) for the other threshold levels of the pollutant as well as for the mean concentration. Finally, multi-pollutant models on which TSP and ozone competed for entry were fitted.

After selection of a final model, interaction terms were constructed of each of the other independent variables with the primary exposure variable - TSP200 or OX10. These were added to the existing models to determine if they significantly improved the fit of the model. None of the interaction terms were significant on any of the models.

For some models, the "through 1977" form of TSP or ozone was selected. For others, the "through 1987" form was selected. For only one model, that relating asthma and OZ10, average annual exceedance frequency from 1977 to 1987 was selected. When the "through 1977" form was selected, the regression model was re-run using the "through 1987" form of the variable to see if it would change the regression coefficient for that variable significantly. It did not. In every case, the 1977 and 1987 forms of exposure variables were highly correlated and were close competitors in the stepwise selection process. We felt, however, that it was best to allow the statistical selection process to choose the form which contributed best to the model rather than to arbitrarily force in one or the other of the forms.



## RESULTS

### Cumulative Incidence of Definite Symptoms and TSP

Descriptive characteristics of the study population and the prevalence rates of individual symptoms are given by Hodgkin (1). Individuals who had definite symptoms in 1977 are excluded from the analyses of this section since C.I. is the outcome. The models selected according to the stepwise multiple logistic regression procedure for association of TSP200 and cumulative incidence of definite symptoms of AOD, chronic bronchitis, and asthma, are shown in Tables 2, 3, and 4, respectively. TSP200 was statistically significantly associated with incidence of the three types of definite symptoms, with relative risks for an increase in average annual exceedance frequency of 1000 hours per year ranging from 1.33 for incidence of chronic bronchitis to 1.74 for incidence of asthma. Possible symptoms of that outcome in 1977 was the most significant predictor of incidence of definite symptoms of each outcome.

Other covariates which were statistically significantly related with one or more of the outcomes were: years smoked in the past, years lived with a smoker, years worked with a smoker, whether or not an individual had definite symptoms of AOD in childhood (before the age of 16), and frequency of childhood colds. Gender, age, and education were forced into each model to adjust for these demographic factors.

The only covariates other than the demographic factors which came into the model for incidence of definite asthma were: years worked with a smoker and prevalence of possible symptoms of asthma in 1977. The smaller number of covariates which entered the model (i.e. were statistically significant) was due to the small number

of cases available for analysis. The fact that only "years worked with a smoker" and "possible symptoms of asthma in 1977" came into the asthma model does not indicate that other covariates were not statistically significantly related to incidence of asthma, but only that these two were the most significantly related and other covariates did not achieve statistical significance once they were in the model. This same principle holds true for the covariates of other models as well.

The final models selected for each outcome were then re-run for each of the other thresholds of total suspended particulates for exceedance frequencies of 60, 100, and 150 mcg/m<sup>3</sup> and for mean concentration. In re-running these final models, the same sets of variables as for TSP200 were used, but the values of the regression coefficients were allowed to change.

Using the methods described by Abbey (5), the relative risks for different increments of average annual hours of ambient concentrations above the threshold were determined for each threshold. The results are shown in Table 5. The regression coefficient for average annual hours in excess of 60 mcg/m<sup>3</sup> was not significantly different from zero for any of the three outcomes, indicating no significantly increased relative risks for this lowest threshold. The corresponding regression coefficients for the thresholds 100, 150, and 200 mcg/m<sup>3</sup>, and mean concentration, were statistically significantly ( $p < 0.05$ ) different from zero for cumulative incidence of AOD, and chronic bronchitis indicating significantly increased relative risks for these thresholds. For asthma, they were significantly different from 0 only for the thresholds 150 and 200 mcg/m<sup>3</sup>.

Using the data from Table 5, "exposure-response" type curves are plotted in Figure 1, showing the relationship between relative risk of ten year cumulative incidence of AOD and increasing threshold levels for fixed average annual hours above the thresholds. Figure 2 shows relative risk contour plots for the cumulative incidence of definite symptoms of AOD and average annual ambient concentrations of TSP. These contour plots show the amounts of average annual ambient concentrations above the thresholds which are associated with several for fixed relative risks. Such contour plots can be useful for standard-setting, as they make possible determination of how many hours of ambient concentrations in excess of a threshold should be allowed if one wishes to keep relative risk to the public below a specified level. In making the curves of Figure 1 and Figure 2, we were careful to avoid extrapolation. All data points are within the range of ambient concentrations experienced by the population.

#### Change in Symptom Severity Score and TSP

The above analyses of cumulative incidence excluded individuals who had definite symptoms in 1977. In order to allow these individuals to be included, we used the change in the symptom severity score between 1977 and 1987 as an outcome variable for each of AOD, chronic bronchitis, and asthma. Stepwise multiple linear regressions were used to determine the form of the models for each of these outcomes for TSP200. Table 6 shows the standardized regression coefficients for the variables selected by the stepwise multiple linear regression for each outcome. Standardized regression coefficients were used in this table as their magnitudes can be directly compared as an indication of strength of association.

The order of entry of each of the variables is also shown in the table. In the initial model setting age, gender, and education were forced into each of the models before the other variables were selected. Then the models were re-run allowing age, gender, and education to compete for entry with those that had been included in the initial models. Results from the latter models are presented in Table 6.

Average annual hours above TSP200 was significantly related to change in severity score for each of the outcomes. With the exception of asthma, by far the strongest associations with change in severity score were the initial 1977 symptoms score. This score has a negative coefficient, indicating that those who had the highest severity scores initially tended to increase their scores less than those who had lower initial scores. This would be expected as there is little possibility of increasing scores (worsening of symptoms) for those who have a high score initially. Education failed to show a statistically significant ( $p < 0.05$ ) association with change in severity score for any of the respiratory symptoms complexes. In addition, gender failed to show a significant relationship with chronic bronchitis and age failed to show a significant relationship with change in severity score for asthma. Three covariates - years smoked, years of dust exposure at work, and years lived with a smoker - were not significantly related to change in severity score for asthma. The distributions of these three covariates for those who developed definite symptoms of asthma and those who did not were compared and found to be similar.

Each of the multiple linear regressions of the changes in symptom score on average annual exceedance frequency for TSP200 were repeated for the other

thresholds of TSP. The respective regression models included the independent variables that had entered into the models displayed in Table 6. All the regression coefficients of pollutant exposure were statistically significant at the 5% level, except for the chronic bronchitis coefficients for TSP60 and TSP100. The magnitudes of the regression coefficients increased and their tail probabilities decreased with increasing threshold levels, indicating that a consistent dose-response type relationship existed.

#### Incidence of Respiratory Symptoms and Ozone

Mean concentration and average annual exceedance frequencies 10, 12, 15, 20, or 25 pphm ozone were not statistically significantly associated with cumulative incidence of any of the respiratory symptoms outcomes, though a trend association ( $p = 0.056$ ) was noted between OZ10 and cumulative incidence of asthma. The multiple logistic regression model for OZ10 and asthma was very similar to that for TSP200 as shown in Table 4. The point estimate of relative risk for ozone was 2.07 (95% confidence interval: 0.98, 4.89), for a 1000 hour average annual increment in OZ10, 1977-1987. It is interesting to note that the 1977-1987 form of OZ10 came into the model indicating that recent ambient concentrations for ozone may be more related to incidence of asthma than past concentrations. In cases where the regression coefficients for ozone exceedance frequency were close to statistical significance, regressions were repeated using excess ozone concentrations above the thresholds instead of exceedance frequencies. The regression coefficients for excess concentrations also failed to show statistical significance.

### Change in Respiratory Symptoms Severity Scores and Ozone.

Change in asthma severity score was significantly associated with mean concentration of ozone (1977-1987) and with the 1977-1987 average annual exceedance frequency only for the thresholds 10 pphm and 12 pphm. The non-standardized regression coefficients were larger for the exceedance frequency OZ12 than for OZ10, implying that on the average fewer hours of ambient concentrations above the higher threshold produced the same effect. The two right most columns of Table 6 display the multiple linear regression models for change in asthma score for the exceedance frequencies TSP200 and OZ10. The sets of variables included in the models and the standardized regression coefficients are quite similar. Change in severity scores for the other respiratory symptoms complexes were not significantly associated with exceedance frequencies for any of the thresholds of ozone or for mean concentration.

Lack of statistical significance for exceedance frequencies above higher thresholds of ozone may be due to lack of a sufficient portion of our study population with enough average annual hours of ambient concentrations above the higher thresholds of ozone. For example, the highest decile of our study population experienced only 243 hours above 15 pphm, 83 hours above 20 pphm, and 23 hours above 25 pphm.

### Exclusion of 1977 Symptoms Score as a Covariate

All of the previous regression models used the 1977 symptoms score as a covariate. For the multiple logistic regression models - which excluded individuals with

definite symptoms in 1977 the covariate took the form of a dummy variable indicating whether or not an individual had possible symptoms in 1977. For each of the respiratory symptoms complexes this covariate had strong and highly statistically significant effects. Since individuals had lived for at least 10 years in their present neighborhoods prior to 1977, it is possible that the development of possible symptoms could be the result of ambient concentrations of air pollution. Thus, to control for possible symptoms as a covariate may dilute the effects of the pollutant variable in the model. To check on this possibility and also the possibility that our models were being unduly influenced by this strong covariate the final multiple logistic regression models of tables 2 through 4 were run again excluding possible symptoms as a covariate. The regression coefficients for TSP changed very little and were each within 5% of their previous value. This process was repeated for the multiple linear regression models summarized in table 6 where the covariate took the form of the 1977 symptoms score. Again regression coefficients changed only slightly, being within 12% of their original values, except for asthma and ozone where the coefficient was 27% smaller. Ozone continued to lack statistical significance in the multiple linear regressions for AOD and chronic bronchitis symptoms scores.

#### **Multi-pollutant Analyses and Respiratory Symptoms**

Change in severity score and incidence of asthma were significantly associated with both total suspended particulates and ozone as indicated by separate single pollutant multiple logistic regression models. To determine whether TSP or ozone was more strongly associated with incidence of asthma, a stepwise multiple logistic

regression for cumulative incidence of asthma was run allowing the exceedance frequencies for the most significant thresholds - TSP200 and OZ10 - to compete for entry. Another regression was run allowing mean concentrations of TSP and ozone to compete for entry. TSP200 (0.06 p to enter) entered the model in preference to OZ10 (0.20 p to enter). On the other hand mean concentration of ozone (0.03 p to enter) entered before the mean concentration of TSP (0.09 p to enter). Thus, we were unable to determine unequivocally whether TSP or ozone were more significantly associated with the incidence of asthma. It appears that they both were.

Both TSP and ozone were also significantly associated with change in severity score for asthma as indicated by separate single pollutant multiple regression models. Hence, a stepwise multiple linear regression was run, again allowing the most significant exceedance frequencies of each pollutant to compete for entry. Then this was repeated using mean concentrations for the two pollutants. TSP200 and OZ10 were again very close competitors, each having a p to enter  $<0.025$ . TSP200 came in before OZ10. For mean concentrations, ozone entered in preference to TSP. The p to enter for ozone was  $<0.025$ , for TSP;  $<0.05$ .

We then examined correlations between TSP and ozone for exceedance frequencies and mean concentrations experienced by our study population. This was done in order to determine if the associations of ozone with asthma observed above might be artifactual due to a high correlation between ozone and TSP. The correlation between the 1973-1987 average annual mean concentrations of ozone and TSP was 0.74. The correlation between the 1973-1987 averages of the exceedance frequencies



OZ10 and TSP200 was 0.72. Correlations between exceedance frequencies for other thresholds of ozone and TSP200 are also high. For example, the correlation between OZ15 and TSP200 is 0.70 and that for OZ20 and TSP200 is 0.66. These higher thresholds of ozone, however, did not show statistically significant associations with the incidence of asthma or changes in severity score for asthma as would be expected if the significant associations observed for the lower thresholds were due only to statistical artifacts. Thus, our data suggests that both TSP and ozone are related to incidence of definite symptoms and change in severity score for asthma.

Once one pollutant was in the model however, the other did not show a statistically significant regression coefficient due to the high correlations between them. In order to test for possible interaction effects we forced both TSP and ozone into the models as well as the product of the two as an interaction term. No statistically significant interactions were observed.

Multi-pollutant analyses were not conducted for the other respiratory symptoms complexes as our data failed to indicate statistically significant associations of ozone with the other respiratory symptom complexes.

## DISCUSSION

### Limitations of Study

The limitations of this study have been discussed by Euler (2). We will only summarize them briefly here.

1. The limitation of cross-sectional studies discussed by Euler (2) is no longer relevant, since we are now studying cumulative incidence in a cohort followed

for ten years rather than prevalence ascertained at one point in time.

2. Inaccuracy of self-reported symptoms may introduce measurement bias to the degree that it may not accurately represent actual presence of symptoms. A validity study was conducted on a sample of 87 subjects from our population. Self-reported symptoms and residence history were validated and pulmonary function tests were performed. The validity of the NHLBI questionnaire was confirmed in this population, as it has been in other populations (6). However, there was a lack of conclusive concurrence between self-reported AOD symptoms and the objective results of spirometry, single-breath oxygen tests, and volume of isoflow pulmonary function tests. These results are reported in detail elsewhere (7). Samet (6) concluded that the discrepancy between the symptoms reported on questionnaires and pulmonary function test results is predictable and should not necessarily detract from the usefulness of these respiratory symptom questionnaires in epidemiological studies. The problem of possible measurement bias may be less severe for ascertaining asthma, since individuals must have been told by their physician that they had asthma as well as having to indicate symptoms.
3. Measurement error in cumulative ambient concentrations may have resulted from our use of interpolations from fixed site monitoring stations. The accuracy of these interpolations is discussed by Abbey (8). The Environmental Protection Agency has recommended distances for each pollutant within which concentrations at fixed site monitoring stations can be considered representative.

As a further check on our results we restricted interpolations to be within the A or B quality range, considered representative by EPA and reran the final regression models using TSP200 and TSP mean concentration as the exposure variables. For TSP this reduced the number of individuals available for analyses by approximately one-half. The regression coefficients were somewhat smaller, but in the same general direction as the previous regression coefficients. The statistical significance of the regression coefficients was in every case less due to the reduced sample size, and did not achieve the .05 level of statistical significance. T tests indicated that cumulative ambient concentrations of TSP were statistically significantly higher for individuals who were within the A or B quality interpolation ranges than for those who lived outside those ranges ( $p < .0001$ ). For example, TSP200 for the time period 1973-1987 averaged 470 hours per year for individuals within the A or B quality interpolation ranges and 341 for individuals with less than B quality data. A similar sensitivity analysis was conducted for ozone and asthma again restricting interpolations to those with A or B quality. Due to the much larger distance considered to be A or B quality for ozone, there was only a slight reduction of approximately 500 subjects in the number available for analyses. As might be expected, the regression coefficients agreed more closely. Again, t-tests indicated lower concentrations for individuals outside the A or B quality interpolation range. It was felt that the reduced sample size and the lack of contrast in cumulative ambient concentrations for those with A or B quality interpolations accounted for the

reduced statistical significance and lower magnitude of regression coefficients.

4. Estimates of air pollution exposure used in this study were estimates of ambient concentrations only. Studying the associations between adverse health effects and ambient concentrations is useful, since ambient concentrations are monitored and air quality standards apply to them. However, actual individual exposures may differ significantly, since individuals are known to spend up to 90% of their time indoors. For example, there are no indoor sources of ozone, and it is known that indoor concentrations of ozone are substantially less than outdoor concentrations (9). It is likely that the actual ozone exposures of our population are considerably less than the estimates of ambient concentrations. A similar problem exists for TSP, although indoor sources of TSP do exist. One of the primary indoor sources of TSP is cigarette smoking, which has been taken into account as a covariate in the present analyses. Our future analyses of these data will attempt to model subjects' exposures more accurately by use of adjustment factors obtained in other human exposure studies. These factors are related to residence, workplace, and lifestyle characteristics ascertained by our survey.

The sources of error mentioned above are likely to make statistically significant associations more difficult to demonstrate (10), as long as they are not systematically biased. Thus, the associations demonstrated for TSP may in reality be even more statistically significant. However, lack of statistical associations with ozone could be due to these and other sources of uncontrolled

variability.

5. There are limitations in statistically separating air pollutants occurring in an ambient mixture. Human chamber studies can more accurately assess the effects of acute exposures of very short durations (11), but they are not feasible for studying long-term cumulative exposures in free-living populations.
6. It is possible that other pollutants in the ambient air may affect the statistical associations found by these analyses. We plan to study the associations between health effects and exposure to  $\text{NO}_2$ ,  $\text{SO}_2$ ,  $\text{SO}_4$ , <2.5 micron fine particulates, and <10 micron particulates.

#### Comparison of Current Results With Previously Published Results

Previously published papers from this study on respiratory symptoms have reported on associations between the prevalence of AOD in 1977 and ambient concentrations of TSP and total oxidants (2,3). The 7,445 subjects available for prevalence analyses in 1977 included non-whites who were not followed in the cohort study (due to small numbers) as well as individuals who have since died or were lost to follow-up. The same thresholds were used for exceedance frequency of TSP and baseline ambient concentrations were cumulated over essentially the same time period - 1973 through 1976 compared to 1973 through March, 1977, for the current analyses. Between 1973 and 1977, total oxidants were being measured at some monitoring stations and ozone was being measured at others; some stations measured both simultaneously for up to several months. The previous study used total oxidants data in preference to ozone data where both were available, but used ozone data if total

oxidants data did not exist. The current study used ozone in preference to total oxidants. However, the high correlations between total oxidants and ozone for all thresholds, as reported by Abbey (8) make it unlikely that this methodological discrepancy would affect results.

The only outcome reported in the previous papers (2,3) was prevalence of definite AOD symptoms. Definite AOD symptoms were defined in the same manner in the current analyses, though in the previous papers this symptoms complex was referred to as Chronic Obstructive Pulmonary Disease (COPD). Results from multiple logistic regression analyses of the prevalence data were in very close agreement with our current results; the average annual exceedance frequency for TSP60 was not significantly associated with prevalence of AOD, but the exceedance frequencies for TSP100, TSP150, and TSP200 were. The point estimates of the relative risks of prevalence for average annual 1000-hour exceedance frequencies TSP100, TSP150, and TSP200 were 1.04, 1.11, and 1.30, respectively; these estimates are very close to the corresponding relative risk point estimates for cumulative incidence, 1.08, 1.15, and 1.35. Euler (3) showed a highly statistically significant association between prevalence of definite AOD symptoms and the average annual exceedance frequencies of OZ10, OZ15, and OZ20 for total oxidants, whereas the current analyses failed to show any statistically significant associations between cumulative ten year incidence of AOD and any of these or other thresholds for ozone.

Euler (3) conducted multi-pollutant multiple logistic regression analyses in which exceedance frequencies for TSP200, OX10, and the 4 pphm threshold of SO<sub>2</sub> were

allowed to enter simultaneously in a single logistic regression. This analysis showed that only TSP was significantly associated with prevalence of definite AOD symptoms. Our current multi-pollutant analyses of cumulative incidence of definite symptoms of AOD indicate that TSP and not ozone is related to this outcome. However, both pollutants appear to be related to incidence and increasing severity of symptoms of asthma. It is also possible that our study population does not include enough subjects exposed long enough to ambient concentrations above the higher thresholds of ozone for statistically significant effects to be detected for AOD.

It is also possible that some other component of the ambient air pollution mix is most directly related to development of AOD symptoms and that total suspended particulates is more highly correlated with this other component than ozone is. Additional pollutants to be used in future analyses include fine particulates in the <2.5 micron range as well as fine particulates in the <10 micron range.

#### **Comparison of Our Findings with Those of Other Investigators**

Several reviews summarizing epidemiologic studies relating ambient air pollution to chronic respiratory disease morbidity have been published recently, and their general conclusion was that ambient air pollution contributes to morbidity from respiratory disease above and beyond that due to cigarette smoking (12,13,14). In this section we compare the results of the present study with the results of several of these studies.

In a previous study of Seventh-day Adventists, Cohen compared the prevalence of respiratory symptom complexes ascertained by the standardized NHLBI respiratory symptoms questionnaire in a group of 136 Seventh-day Adventists living in the San

Gabriel Valley (high pollution area) and a group of 207 living in San Diego (low pollution area (15). 89.5% of study subjects had lived in the area of their present residence for five years or longer and 78.1% for ten years or longer. The ascertainment of symptoms was made in January, 1970. There were no statistically significant differences between the two areas in prevalence of any of the pulmonary function parameters tested. The low prevalence rates for respiratory symptom complexes which Cohen observed in this non-smoking population would make it difficult to show statistically significant differences, since the sample sizes of his study were much smaller than ours. Cohen also did not adjust for such possibly confounding factors as passive smoking and occupational exposure to air pollutants as we have. As Cohen noted, as of 1970 his subjects may not yet have been exposed to elevated ambient concentrations of ozone long enough to cause deleterious effects.

The AHSMOG study area includes the South Coast Air Basin which has the most severe oxidant air pollution in the United States (16). Three cities within or adjacent to this air basin - Burbank, Lancaster, and Long Beach, California - had average daily maximum one-hour total oxidant concentrations of 9.0, 6.5, and 3.7 pphm respectively over the years 1972-1977. Prevalence of chronic respiratory symptoms in another study, however, did not consistently increase with increasing average total oxidant concentrations (17). In another study, a comparison of office workers in Los Angeles (average maximal one-hour oxidant concentration = 7 pphm) and San Francisco (average maximal one-hour oxidant concentration = 2 pphm), answers to the NHLBI questions concerning cough and sputum production were similar in both cities.



However, non-chronic cough during "bad weather" was more common in the Los Angeles women, as was sputum production (16).

Detels (18) compared cohorts of never-smoking residents in Lancaster, a city just outside the South Coast Air Basin to those of Glendora, a city of high ambient concentrations within the basin. Each cohort consisted of approximately 1,000 individuals. Lung function tests and ascertainment of respiratory symptoms were performed twice in each community at intervals of approximately five years. Lancaster experienced moderate levels of ozone and low levels of other pollutants, while Glendora experienced high levels of ozone and relatively high levels of sulfates and particulates. Although most of the lung function tests showed significantly more rapid declines in functions among adults in Glendora, there were no consistently statistically significant differences in the incidence of cough, sputum production, wheezing, or physician diagnosis of asthma, bronchitis, and/or emphysema. The proportions of asymptomatic individuals in the two communities becoming symptomatic during the five-year interval was similar; so were the proportions of symptomatic individuals becoming asymptomatic. The annual averages of peak hourly values of total oxidants for Lancaster and Glendora were 7 pphm and 11 pphm, respectively, but the annual mean concentrations were very similar. For example, the 1985 annual mean concentrations were 4.0 pphm for Lancaster and 3.6 pphm for Glendora. The annual average concentrations of TSP were 85 mcg/m<sup>3</sup> for Lancaster and 133 mcg/m<sup>3</sup> for Glendora.

Because of selection of some individuals from lower pollution areas, subjects in our cohort experienced a wider range of ambient concentrations, with annual mean

concentrations of TSP ranging from 56 mcg/m<sup>3</sup> for the lowest decile to 135 mcg/m<sup>3</sup> for the highest decile. Mean levels of ozone ranged from 1.1 pphm for the lowest decile of our cohort to 2.4 pphm for the highest decile and this tended to be lower than for Detel's study. Our lack of a larger number of subjects at higher levels of ambient ozone concentrations may explain the failure of our study to show statistically significant associations between ozone and respiratory symptoms other than asthma or for asthma and thresholds of ozone above 12 pphm. The subjects of our study may have experienced elevated ambient concentrations of air pollutants for longer periods, since they had lived ten years or longer in their present neighborhoods at the time of the baseline survey. Our study subjects were then followed for a longer time period - ten years, instead of only five. The ten year follow-up period of our study may have allowed greater time for the development of symptoms.

Comstock (19) studied more than 1,000 telephone workers, most of whom worked outdoors, in four different areas of the eastern U.S. He tested the lung function of these subjects and ascertained the prevalence of respiratory symptoms using the standard questionnaire. Some of the workers lived in areas with low air pollution, some in areas with high air pollution. The sample also included 600 telephone workers in Tokyo. The prevalence of symptoms was initially ascertained in 1962/1963 in the U.S. and again five to six years later and was ascertained once in Tokyo in 1967. There was a slight elevation of respiratory symptom prevalence, but no difference in parameters of lung function for subjects in New York, the most polluted area. Comstock did not report on the cumulative incidence of symptoms.

Sawicki (20) conducted a five year cohort study contrasting residents of less polluted and more polluted areas of Cracow, Poland. Average annual TSP levels at the beginning of the study were 90 mcg/m<sup>3</sup> in the less polluted area and 170 mcg/m<sup>3</sup> in the more highly polluted area. Prevalence of respiratory disease was reported at the beginning and the end of the study period, but cumulative incidence was not reported. Initial prevalence of chronic bronchitis in the polluted area was significantly higher for both smoking and non-smoking men, but not for women. The initial prevalence of asthma was also higher among smokers living in the more polluted area. At the time of follow-up, prevalence of respiratory disease was also higher in the more polluted area for many of the age, race, and sex groups studied. Also, the prevalence of chronic obstructive pulmonary disease was higher for present smokers living in the more highly polluted areas. These results are consistent with our findings, though they are not directly comparable to them.

Ferris (21,22) administered the standardized respiratory symptoms questionnaire to a cohort of approximately 800 subjects in the pulp mill town of Berlin, New Hampshire in 1961, 1967 and 1973. The annual average level of TSP decreased from 180 to 131 to 80 mcg/m<sup>3</sup> over these three points in time. Respiratory symptom rates standardized for age and sex decreased between 1961 and 1967, but they did not change significantly between 1967 and 1973.

Ware (14) has reviewed a number of studies of chronic bronchitis and other respiratory symptoms which have reported average levels of TSP and SO<sub>2</sub>. One study by Hammer (23) noted effects on respiratory symptoms with an annual mean

concentration of TSP of 135 mcg/m<sup>3</sup>. Several studies noted effects for average mean levels above 180 mcg/m<sup>3</sup>. As average levels of TSP increase over the different studies, the levels of SO<sub>2</sub> increased also, making it difficult to separate the effects of the two pollutants. Average annual levels of SO<sub>2</sub> in our study areas are below 25 mcg/m<sup>3</sup>, in contrast to the average levels for the studies reported by Ware which range from 55 mcg/m<sup>3</sup> upward. Since levels of SO<sub>2</sub> are relatively low in our population, we hope to be able to separate the effects of TSP and SO<sub>2</sub> on cumulative incidence. Effects of SO<sub>2</sub> will be addressed in future papers, though Euler (2), reporting on the effects of TSP and SO<sub>2</sub> on prevalence of respiratory symptoms in our population, noted much stronger effects of TSP than of SO<sub>2</sub>. He found that less than 9% of the variation in SO<sub>2</sub> was explained by TSP. In a subsequent multivariate analysis (3) of TSP, total oxidants, and SO<sub>2</sub>, he found the prevalence of definite AOD symptoms to be significantly associated with TSP but not total oxidants and SO<sub>2</sub>.

Ware (14) comments on the difficulty of assessing health effects at annual average levels of TSP lower than 180 mcg/m<sup>3</sup> because of anticipated smaller rates of health effects and confounding effects of other factors which vary over communities. Advantages of our population include the homogeneous nature of the cohort and the large number of other lifestyle factors measured, which make possible the assessment of health effects at lower ambient concentrations.

In summary, our study has determined statistically significant increased risks of incidence associated with long-term exposures to elevated concentrations of TSP. Increased risks of AOD and chronic bronchitis are associated with exposure to TSP

above 100 mcg/m<sup>3</sup> and increased risks of asthma with exposures above 150 mcg/m<sup>3</sup>. Long-term ambient concentrations of ozone in excess of 10 pphm ozone were significantly associated with increases in the severity of asthma. These results need to be considered in future decisions regarding standard settings of both TSP and ozone.

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**Table 1.-Descriptive Statistics for Candidate Independent Variables for Stepwise Regressions For Incidence or Change in Score of Definite AOD Symptoms, Chronic Bronchitis Symptoms, and Asthma.  
(n = 3914)**

<u>Mean</u>	<u>Max. Value</u>	<u>% = 0</u>	
-	-	36.0	<u>Primary Variables</u> (Forced Into Regressions)
55.9	95	-	Gender (0 = males, 1 = females)
13.9	19	-	Age - April 1, 1977
			Years Education - 1977
			<u>Secondary Variables</u>
			<u>Ambient Air Pollutants</u>
394.6	2277	2.0	TSP (Average annual hours in excess of 200 mcg/m <sup>3</sup> 1973-1987).
455.9	2484	11.0	TSP (Average annual hours in excess of 200 mcg/m <sup>3</sup> 1973-1977).
368.6	2190	8.0	TSP (Average annual hours in excess of 200 mcg/m <sup>3</sup> 1977-1987).
337.0	966	0.0	Ozone (Average annual hours in excess of 10 pphm 1973-1987).
335.3	1044	0.0	Ozone (Average annual hours in excess of 10 pphm 1973-1977).
337.8	1083	0.0	Ozone (Average annual hours in excess of 10 pphm 1977-1987).
			<u>Past and Passive Smoking</u>
14.8	58	84.6	Years smoked in the past.
21.3	72	70.0	Years lived with a smoker until 1977.
6.1	10	94.0	Years lived with a smoker, 1977-1987.
22.3	72	69.4	Years lived with a smoker until 1987.
-	-	97.5	Whether or not currently living with a smoker in 1987. (0 = no, 1 = yes)
11.5	57	60.3	Years worked with a smoker until 1977.
4.9	10	82.7	Years worked with a smoker, 1977-1987.
12.9	57	57.9	Years worked with a smoker until 1987.
-	-	95.5	Whether or not currently working with a smoker in 1987. (0 = no, 1 = yes)
			<u>Occupational Air Pollutants</u>
16.5	69	88.7	Years of dust exposure at work until 1977.
4.3	10	92.9	Years of dust exposure at work, 1977-1987.
19.3	79	87.6	Years of dust exposure at work until 1987.
-	-	90.1	Whether or not currently exposed to dust at work in 1987. (0 = no, 1 = yes)
16.1	70	86.8	Years of fume exposure at work until 1977.
4.1	10	91.6	Years of fume exposure at work, 1977-1987.
18.7	75	85.5	Years of fume exposure at work until 1987.
-	-	89.7	Whether or not currently exposed to fumes at work in 1987 (used only in ozone analyses). (0=no, 1 = yes)
			<u>Previous Respiratory Symptoms</u>
2.5	5	-	Frequency of childhood colds (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
-	-	91.8	Childhood definite symptoms of AOD before age of sixteen.(0 = no, 1 = yes)
-	-		Whether or not had possible symptoms of outcome variable in 1977:
-	-	14.9	AOD (0 = no, 1 = yes)
-	-	14.7	Bronchitis (0 = no, 1 = yes)
-	-	1.2	Asthma (0 = no, 1 = yes)
			1977 symptoms score for outcome variable:
1.39	26	72.6	AOD (0 = no symptoms)
1.08	10	75.2	Bronchitis (0 = no symptoms)
0.27	10	95.4	Asthma (0 = no symptoms)

**Table 2.-Multiple Logistic Regression for Cumulative Incidence of Definite Symptoms of AOD, 1977-1987, with Hours Average Annual Concentration In Excess of 200 mcg/m<sup>3</sup> of TSP as the Air Pollution Exposure Variable.**

(n = 3,220, incident cases = 272, definite cases in 1977 excluded)

<u>Variable</u>	<u>Regression Coefficient</u>	<u>Increment<sup>(1)</sup></u>	<u>Relative Risk<sup>(5)</sup></u>	<u>95% C.I. for Relative Risk</u>
TSP (Hrs. in Excess of 200 mcg/m <sup>3</sup> <sup>(2)</sup> )	0.0003339**	1000 hr/yr.	1.36	1.11, 1.85
Years Smoked	0.022531*	10 yr.	1.23	1.05, 1.55
Years Lived with Smoker <sup>(3)</sup>	0.013211*	10 yr.	1.13	1.03, 1.29
Years Worked with Smoker <sup>(4)</sup>	0.013362*	10 yr.	1.13	1.01, 1.32
Possible Symptoms in 1977	0.65389***	(0 = No, 1 = Yes)	1.77	1.58, 2.47
Childhood AOD	0.30528**	(0 = No, 1 = Yes)	1.31	1.09, 1.78
Childhood Colds	0.24882**	1	1.26	1.09, 1.55
Gender	0.096189	(0 = F, 1 = M)	1.09	0.96, 1.30
Age	-0.0022017	10 yr.	0.98	0.88, 1.10
Education	0.015347	4 yr.	1.06	0.88, 1.35
Constant	-2.9313			

(1) Increment for computations of relative risks.

(2) Average annual hours in excess of 200 mcg/m<sup>3</sup> 1973-1987.

(3) Years lived with smoker through 1977.

(4) Years worked with smoker through 1987.

(5) Relative risk of increase in exposure of one increment, holding other variables in model constant.

\* p < .05; \*\* p < .01; \*\*\* p < .001.

**Table 3.-Multiple Logistic Regression for Cumulative Incidence of Definite Chronic Bronchitis Symptoms, 1977-1987, with Hours Average Annual Concentration In Excess of 200 mcg/m<sup>3</sup> of TSP as the Air Pollution Variable.**

(n = 3,310, incident cases = 234, definite cases in 1977 excluded)

<u>Variable</u>	<u>Regression Coefficient</u>	<u>Increment<sup>(1)</sup></u>	<u>Relative Risk<sup>(5)</sup></u>	<u>95% C.I. for Relative Risk</u>
TSP (Hrs. in Excess of 200 mcg/m <sup>3</sup> <sup>(2)</sup> )	0.00030683*	1000 hr/yr.	1.33	1.07, 1.81
Years Smoked	0.028107**	10 yr.	1.30	1.11, 1.63
Years Lived with Smoker <sup>(3)</sup>	0.015471**	10 yr.	1.15	1.05, 1.32
Possible Symptoms in 1977	-0.61393***	(No, Yes)	1.81	1.58, 2.19
Childhood Colds	0.42401***	(No, Yes)	1.37	1.17, 1.66
Gender	0.17227*	(F, M)	1.17	1.02, 1.42
Age	0.0030717	10 yr.	1.03	0.92, 1.17
Education	0.014346	4 yr.	1.05	0.87, 1.34
Constant	-3.7835			

(1) Increment for computations of relative risks.

(2) Average annual hours in excess of 200 mcg/m<sup>3</sup> 1973-1987.

(3) Years lived with smoker through 1977.

(4) Years worked with smoker through 1987.

(5) Relative risk of increase in exposure of one increment, holding other variables in model constant.

\* p < .05; \*\* p < .01; \*\*\* p < .001.

**Table 4.-Multiple Logistic Regression for Cumulative Incidence of Definite Symptoms of Asthma, 1977-1987, with Hours Average Annual Concentration In Excess of 200 mcg/m<sup>3</sup> of TSP as the Air Pollution Variable.**

(n = 3,615, incident cases = 80, definite cases in 1977 excluded)

<u>Variable</u>	<u>Regression Coefficient</u>	<u>Increment<sup>(1)</sup></u>	<u>Relative Risk<sup>(2)</sup></u>	<u>95% C.I. for Relative Risk</u>
TSP (Hrs. in Excess of 200 mcg/m <sup>3</sup> <sup>(3)</sup> )	0.0005687*	1000 hr/yr.	1.74	1.11, 2.92
Years Worked with Smoker <sup>(4)</sup>	0.040998***	10 yr.	1.50	1.23, 1.87
Possible Symptoms in 1977	2.0411***	(No, Yes)	5.02	4.04, 49.03
Gender	-0.30100*	(F, M)	0.74	0.69, 0.80
Age	-0.016371	10 yr.	0.85	0.70, 1.04
Education	0.030878	4 yr.	1.13	0.77, 1.70
Constant	-2.2464			

(1) Increment for computations of relative risks.

(2) Relative risk of increase in exposure of one increment, holding other variables in model constant.

(3) Average annual hours in excess of 200 mcg/m<sup>3</sup> 1973-1987.

(4) Years worked with smoker through 1987.

\* p < .05; \*\* p < .01; \*\*\* p < .001.

**Table 5.-Estimates of Relative Risk for Definite Symptoms of AOD, Chronic Bronchitis, and Asthma From Multiple Logistic Regression for Different Incremental Increases of Exposure Above Various Threshold Levels of Total Suspended Particulates**

<u>Threshold Level</u>	<u>Percent Population Exposed</u>	<u>Increment<sup>(1)</sup> Size (Hrs. Per Year)</u>	<u>Relative Risk Estimate</u>		
			<u>AOD</u>	<u>Chronic Bronchitis</u>	<u>Asthma</u>
60 mcg/m <sup>3</sup>	100	250	1.01	1.01	1.01
	100	500	1.03	1.03	1.03
	99.5	1000	1.06	1.06	1.05
	95	2500	1.14	1.15	1.14
	70	5000	1.31	1.31	1.29
100 mcg/m <sup>3</sup>	98	250	1.02*	1.02*	1.03
	92	500	1.04*	1.04*	1.05
	80	1000	1.08*	1.08*	1.11
	60	2500	1.21*	1.20*	1.29
	18	5000	1.46*	1.44*	1.67
150 mcg/m <sup>3</sup>	73	250	1.04**	1.04*	1.05*
	64	500	1.07**	1.07*	1.11*
	42	1000	1.15**	1.15*	1.23*
	18	2500	1.42**	1.41*	1.66*
200 mcg/m <sup>3</sup>	56	250	1.08***	1.08*	1.15*
	29	500	1.16***	1.16*	1.32*
	11	1000	1.35***	1.35*	1.74*
Mean Concentration	87	60	1.39*	1.36*	1.56
	77	75	1.51*	1.46*	1.74
	59	100	1.72*	1.66*	2.08
	24	120	1.91*	1.83*	2.41
	10	135	2.07*	1.96*	2.68

\* Regression coefficient from which relative risks are calculated is statistically significant (p < .05\*), (p < .01\*\*), (p < .001\*\*\*)

<sup>(1)</sup> Increment for computations of relative risk. Hours per year 1/1/73 through 3/31/77.

Table 6.-Linear Regression Models for Change in Symptoms Scores

Variable	Total Suspended Particulates						Ozone	
	AOD (N = 3,661)		Chronic Bronchitis (N = 3,680)		Asthma (N = 3,697)		Asthma (N = 3634)	
	Entry Order	Standardized Reg. Coeff. (1)	Entry Order	Standardized Reg. Coeff. (2)	Entry Order	Standardized Reg. Coeff. (3)	Entry Order	Standardized Reg. Coeff. (3)
1977 Symptoms Score	1	-0.27	1	-0.50	5	-0.05	4	-0.053
Childhood Colds	2	0.08	2	0.08	6	0.05	5	0.048
AOD Before Age 16	3	0.09	8	0.03	2	0.08	2	0.081
Years Smoked	4	0.07	4	0.05	No(6)		No(6)	
Age	5	0.06	3	0.08	8	-0.01	8	-0.011
Years Worked with Smokers	6(5)	0.06	9(5)	0.03	1(5)	0.09	1	0.094
Years Dust Exposure at Work	7(4)	0.07	5(4)	0.06(6)	No(6)		No(6)	
Gender (0 = male, 1 = female)	8	-0.05	10	-0.02	3	-0.05	3	0.052
TSP200	9(5)	0.04	7(4)	0.04	4(5)	0.05	6	0.042(7)
OZ10								
Years Lived with Smoker	10(4)	0.04	6(4)	0.04	No(6)		No(6)	
Education (Yrs.)	11	-0.01	11	-0.002	7	-0.02	7	-0.015
Achieved R <sup>2</sup>		0.09		0.25		0.02		0.02

(1) All regression coefficients were statistically significant ( $p < .05$ ) except for education.

(2) All regression coefficients were statistically significant ( $p < .05$ ) except for gender and education.

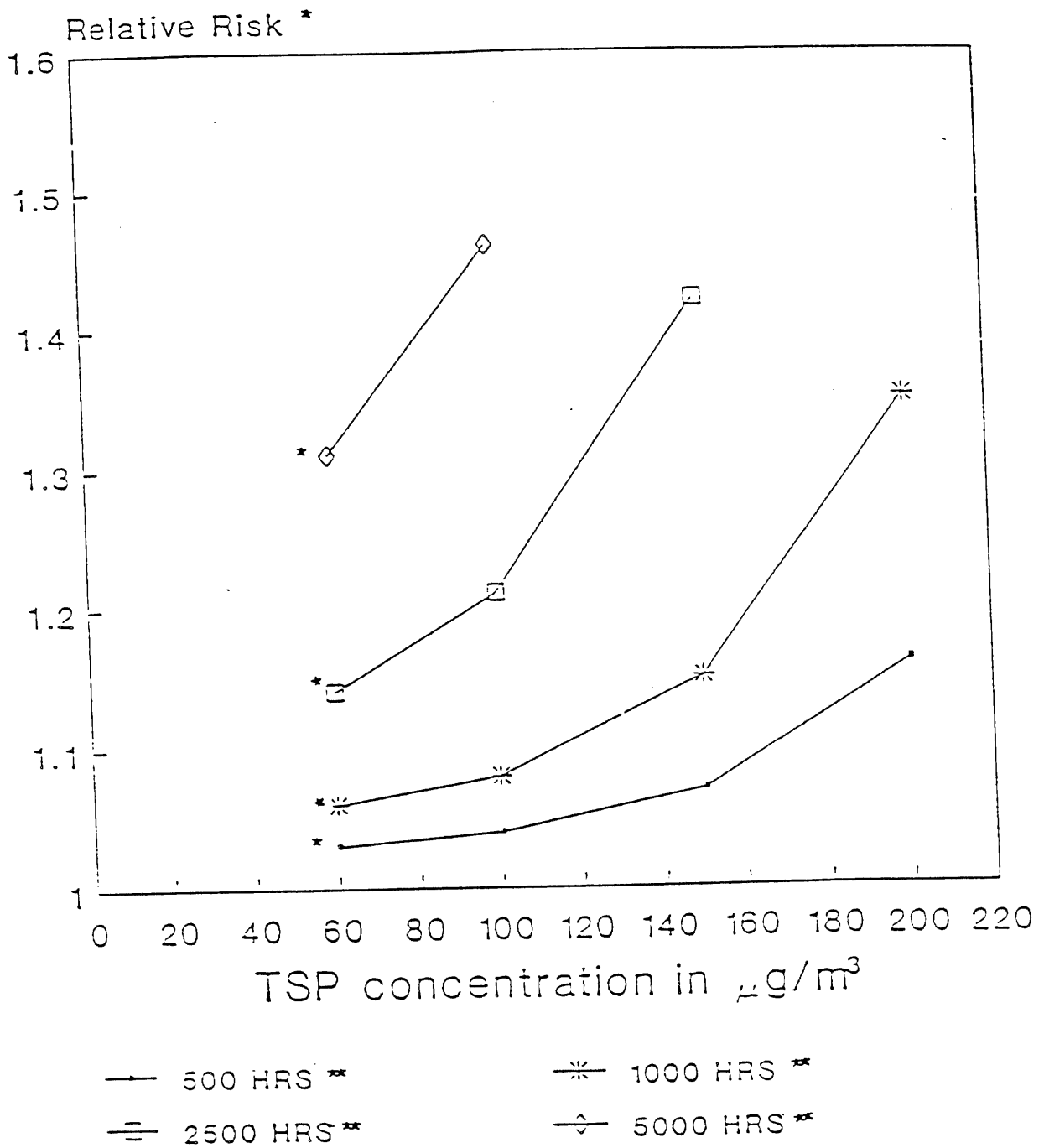
(3) All regression coefficients were statistically significant ( $p < .05$ ) except for age and education.

(4) Average of 1973-1977. These models were re-run using average 1973-1987. Standardized regression coefficients were the same or within 0.01, and their statistical significance was unchanged.

(5) Average 1973-1987.

(6) Did not enter.

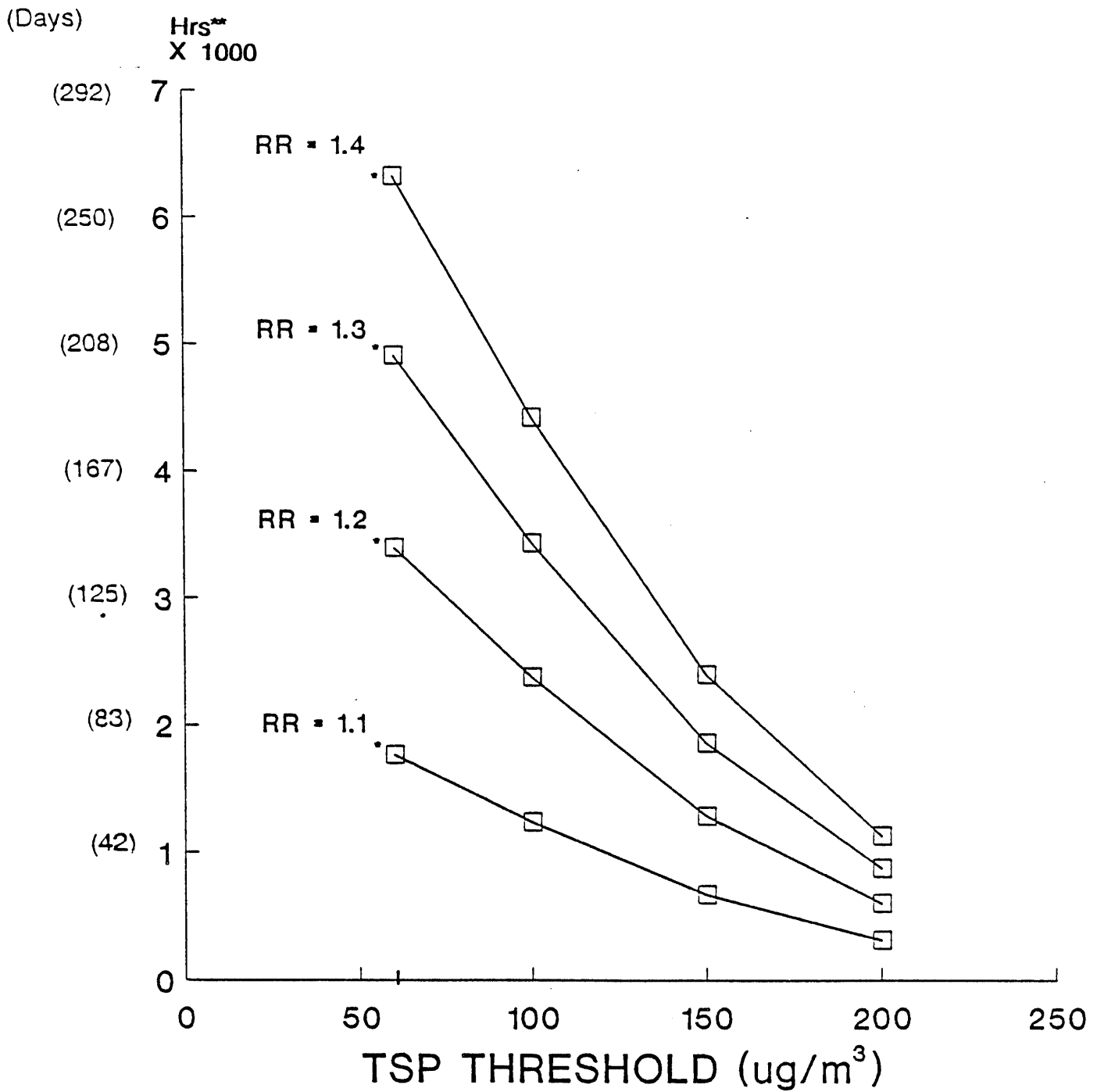
(7) Average 1977-1987.



\* Risks for Lowest Thresholds Not Statistically Significant  
 \*\* Average Annual Hours 1973-1977

Fig. 1. Relative Risk of Cumulative Incidence (1973-1987) of Definite Symptoms of Airway Obstructive Disease for Differing Annual Average Hours (1973-1987) in Excess of 60, 100, 150, and 200  $\text{mcg}/\text{m}^3$  Of Total Suspended Particulates





\* Relative Risks for Lowest Threshold - Not Statistically Significant.  
 \*\* Average Annual Hours 1973-1977.

**Fig. 2. Relative Risk Contour Plots for Incidence of Definite Symptoms of AOD Associated with TSP**



**LONG TERM AMBIENT CONCENTRATIONS OF TOTAL SUSPENDED  
PARTICULATES AND OXIDANTS AS RELATED TO INCIDENCE  
OF CHRONIC DISEASE IN CALIFORNIA SEVENTH-DAY ADVENTISTS**

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## ABSTRACT

Cancer incidence and mortality in a cohort of 6,000 non-smoking California Seventh-day Adventists was monitored for a six year period and relationships with long term cumulative ambient air pollution were observed. Total suspended particulates (TSP) and ozone (OZ) were measured in terms of number of hours in excess of several threshold levels corresponding to national standards as well as mean concentration. For all malignant neoplasms among females, risk increased with increasing exceedance frequencies of all thresholds of TSP except the lowest one, and those increased risks were highly statistically significant. For respiratory cancers, increased risk was associated with only one threshold of OZ and this result was of borderline significance.

Respiratory disease symptoms were assessed in 1977 and again in 1987 using the NHLBI respiratory symptoms questionnaire on a subcohort of 3,914 individuals. Multivariate analyses which adjusted for past and passive smoking, and occupational exposures, indicated statistically significantly ( $p < 0.05$ ) elevated relative risks ranging up to 1.7 for incidence of asthma, definite symptoms of airway obstructive disease (AOD), and chronic bronchitis with TSP in excess of all thresholds except the lowest one but not for any thresholds of ozone. A trend association ( $p = 0.056$ ) was noted between the threshold of 10 pphm ozone and incidence of asthma. These results are presented within the context of standards setting for these constituents of air pollution.

## INTRODUCTION

Previous epidemiological studies of adverse health effects associated with long-term ambient air pollution have been difficult to conduct in most human populations due in large part to the confounding effects of cigarette smoking. However, several studies of air pollution and health have been completed using the Seventh-day Adventist population of California, a non-smoking population which experiences a wide degree of variation in exposure to several ambient air pollutants. For example, Hodgkin et al. demonstrated a statistically significant fifteen per cent increase in prevalence of symptoms of airway obstructive disease (AOD) in non-smoking Adventists who had lived for 10 or more years in an area of high pollution (the South Coast Air Basin of California) compared to those residing 10 years or longer in less heavily polluted areas of the state. This result persisted in a multivariate analysis which controlled for age, sex, race, education, adverse occupational exposures and past smoking history (1). Using this same population, Euler demonstrated statistically significant increased risk of AOD associated with both ambient levels of sulfur dioxide (SO<sub>2</sub>) and total suspended particulates (TSP) (2). A later study also demonstrated statistically significant elevated AOD risk associated with ambient levels of total oxidants but not ambient levels of nitrogen dioxide (3).

These studies have been useful contributions in that they have demonstrated significant alterations in risk associated with long-term ambient concentrations of the pollutants in a non-smoking population and have quantified that risk in reference to numbers of hours in excess of various thresholds of ambient air pollutants corresponding to state and national standards. However, they have been restricted to the analysis of the cross-sectional data then available in which respiratory symptoms data recorded by questionnaire at one point in time (1977) were correlated with ambient air pollutants levels during previous years. Longitudinal data are now available for this population for a six year period of follow-up (1977-82) during which cancer incidence data and cardiovascular disease data were gathered in a prospective manner. Respiratory symptoms were ascertained on a sub-cohort in 1977 and again in 1987 enabling incidence of respiratory symptoms complexes to be ascertained. Mortality data are available for a ten year follow-up period (1977-1986). Additionally, data on ambient levels of additional pollutants also have

been collected (including SO<sub>2</sub>, SO<sub>4</sub>, and fine particulates less than 10 microns and less than 2.5 microns).

Recent papers describe the analysis of the longitudinal data regarding several thresholds of ambient levels of total suspended particulates (TSP) and ozone (OZ) as they are related to definite symptoms of AOD, definite symptoms of chronic bronchitis, asthma, and cancer (Mills submitted, Abbey submitted). This paper summarizes those results and extends the disease outcomes to include cardiovascular disease and all natural cause mortality.

### METHODS

This is a prospective epidemiological study involving approximately six thousand Seventh-day Adventists living in California in 1976 who were participants in the Adventist Health Study (4) and who had resided within five miles of their current residence for at least ten years. By church proscription, Adventists do not smoke although some members of this cohort (36% males, 14% females) smoked prior to joining the church. In addition to completing a detailed lifestyle questionnaire in 1976, members of this cohort completed the NHLBI respiratory symptoms questionnaire in April of 1977. This 1977 questionnaire also elicited detailed lifetime residential histories which were used to construct air pollution profiles for study participants. Measures of ambient concentrations of TSP and ozone in those areas of California inhabited by members of the cohort were provided by the California Air Resources Board for the period 1966-1987. In the earlier years of this time period total oxidants were monitored. Between 1973 and 1980 ozone monitors replaced the total oxidant monitors. However, in a validation study conducted by Abbey (Abbey submitted), mean concentrations of total oxidants and ozone over a two year period were found to have a correlation of 0.94. Measurements of these pollutants were made at several hundred air monitoring stations throughout the state using methods satisfying the Environmental Protection Agency (EPA) standards in effect at the time of monitoring. For each study participant, levels of air pollutants at zip code centroids were estimated for each month of residence since 1966 by utilizing data from the three nearest monitoring stations. An interpolation method was then used to create individual ambient air pollution profiles based on zip code by month residence histories. Details of how these data

were generated and validation studies of the methods are described by Abbey (5, and Abbey submitted). Thus each member of the study cohort had been carefully characterized as regards lifestyle habits, residential history and ambient concentration of several air pollutants.

Between 1977 and 1982 the cohort was followed-up and monitored for newly diagnosed cancer and myocardial infarction. Details of the follow-up procedure have been described by Beeson (4). Mortality follow-up of the cohort has been completed through 1986. The analyses presented in this report concerns risk of cancer, myocardial infarction (1977-1982) and all natural cause mortality (1977-1986) as they were related to long term ambient concentrations of TSP and O<sub>3</sub>. Moreover, the respiratory symptoms questionnaire was completed again in April of 1987 by approximately 85% of the surviving members of the 1977 cohort. Results of the analysis of TSP and O<sub>3</sub> as regards incidence of definite symptoms of airway obstructive disease, chronic bronchitis, and asthma (1977-1987) are also presented in this report. The size and nature of the various sub-cohorts discussed in this report (which are not mutually exclusive) are summarized in Table 1.

#### STATISTICAL ANALYSIS

Frequency distributions of the pollutants inside and outside SCAB were examined in order to create cutpoints for the tertile categories used in preliminary age and sex adjusted stratified Mantel-Haenszel analysis. The cutpoint used in creating the lowest exposure category for both pollutants was taken to be that level experienced by 90% of the study population residing outside the SCAB. The middle and upper tertiles were then created by dichotomizing the remainder of the study population. After these tertiles were identified, age and sex adjusted relative risks and 95% confidence intervals were calculated for each level of the pollutant using the adaptation of the Mantel-Haenszel method for person-years data (6). Trend p-values were also calculated to determine the significance of dose-response relationships in the data. These preliminary stratified analyses were conducted as a check on the results of the final more sophisticated multivariate models since they do not make any assumptions about linear or additive effects.

Cox proportional hazards regression models were constructed which incorporated, in addition to age and



sex, several other covariates which were deemed potentially confounding. The terms included in the final models depended on the disease outcome of interest. Examples of additional covariates include total years of past smoking, educational attainment and exposure to passive smoke at home or work. The specific covariates included in each model are presented in the footnotes to the tables.

For the stratified analyses and the multivariate analyses various threshold levels as well as mean concentration of TSP and OZ (1973-1977) were (separately) used as the main exposure variables in relation to risk of disease during the follow-up period which commenced in April of 1977. As a check, however, the final Cox models were re-run using the time period 1966 through 1977 as the exposure variable for both pollutants. In no case were significant discrepancies in results noted. The time period 1973-1977 was used in preference to 1966-1977 as all study participants had lived 10 years or longer in their present neighborhoods and it was felt that interpolations for the later time would be more accurate due to a larger network of monitoring stations during later years.

In the Cox models, for each of the disease outcomes except all natural cause mortality, age was used as the time variable in the model since age is more closely related to risk of disease than time on study (6). However, since we have detected time trends in mortality probably due to a "Healthy Volunteer Effect" in this data set (4), we used time on study as the time variable in the Cox models for the mortality analysis and incorporated age (as of 4/1/77) as a covariate in the models.

As a check on the proportionality requirement of the Cox model, log-log plots were created and the hazard function was examined across strata of covariates. In no case was there cross-over in the hazard function, indicating that the Cox model was an appropriate choice.

For the respiratory symptoms outcomes the multiple logistic regression model was used since date of incidence was not recorded. Stepwise procedures were used to select statistically significant covariates.

#### **DEFINITION OF DISEASE OUTCOMES**

Associations with ambient levels of TSP and OZ were made with several disease outcome categories including all malignant neoplasms (ICDO, 140-200) in males, all malignant neoplasms in

females, respiratory cancer (ICDO, 160-165), definite myocardial infarction, and all natural cause mortality (ICD9 000-799). The occurrence of incident myocardial infarction was documented by careful review of hospital records including cardiac enzymes and electro cardiographic readings by a cardiologist on the study staff. For the first four of these outcomes, incident events were considered for the time period 4/1/77 through 12/31/82. Since mortality ascertainment of the cohort had been extended through 1986 at the time this analysis was initiated, the follow-up period for the analysis of all natural cause mortality included 4/1/77 through 12/31/86. To ascertain cumulative incidence of respiratory symptoms, the standardized NHLBI questionnaire was administered to study participants in April of 1977 and again in April of 1987. Computer algorithms were applied to the 21 respiratory symptoms questions on this questionnaire to classify individuals as having none, possible, or definite symptoms for each of--chronic bronchitis, asthma, emphysema, or any or all of the above which is termed airway obstructive disease (AOD). An incident case for a particular respiratory symptoms complex was defined as having definite symptoms for that respiratory symptoms complex in 1987 but not having definite symptoms in 1977. To be classified as having "definite" chronic bronchitis, individuals must have had symptoms of cough, and/or sputum production on most days, for at least three months per year for two years or more. For a diagnosis of definite asthma, individuals must have been told by their physician that they had asthma, as well as having a history of wheezing. For emphysema, subjects must have been told by their physician that they had emphysema, as well as having shortness of breath when walking or exercising. Individuals not meeting the criteria for "definite" symptoms for a respiratory symptoms complex, but having some respiratory symptoms associated with that complex, were classified as "possible". Due to an insufficient number of incident cases of emphysema to warrant separate analyses, emphysema was not analyzed as a separate outcome but it was included under airway obstructive disease. Further details on the respiratory symptoms algorithms are provided by Abbey (7). Hodgkin (1) lists the respiratory symptoms which were used and gives the percentage of individuals having each symptom.

## LEVELS OF TSP AND OZ IN THE STUDY AREA

Four threshold levels of TSP corresponding to state of California or national standards are graphically represented in Figure 1 which also shows the proportion of the study population which experienced several levels of hours in excess of these thresholds during the years 1973-1977. As expected, a relatively large proportion of the study population experienced several hundreds of hours in excess of the lowest threshold (THR60, i.e. 60 mcg/m<sup>3</sup> of total suspended particulates) whereas relatively few experienced many hours in excess of the highest threshold, THR200. However, it should be noted that 23% of the study population experienced one thousand hours or more in excess of THR200, which served as our primary threshold for analytic purposes.

In Figure 2 a similar pattern of hours in excess of several threshold levels of OZ is seen. In this case, our primary analytic threshold was OHR10 (i.e. 10 pphm of OZ) and approximately 43% of the study population experienced five hundred hours in excess of this level of OZ, 1973-1977. As regards mean concentration of TSP and OZ, the distribution of these pollutants in the study population are graphically presented in Figures 3 and 4. It should be noted that in these figures individuals with more than 20% missing monthly values have been excluded and that the numeric values of the pollutants refer to the upper boundaries of the intervals.

## TSP AND OZ AS RELATED TO CANCER INCIDENCE, MYOCARDIAL INFARCTION AND ALL NATURAL CAUSE MORTALITY

In this section we review and summarize results concerning TSP and OZ as they were related to cancer incidence, myocardial infarction incidence and all natural cause mortality in the cancer incidence population. Rather than relying upon mean concentration of ambient air pollutants only, these analyses also evaluated numbers of hours in excess of several thresholds of ambient air pollutants as they were related to disease risk. These thresholds corresponded to various State of California and national standards. For TSP these thresholds were 60, 100, 150, and 200 mcg/m<sup>3</sup>. Table 2 summarizes relative risks for a 1000 hour per year average annual increase in ambient concentration above TSP200, the most statistically significant threshold. Our results indicated that, for all malignant neoplasms among females,

statistically significant increases in cancer risk were associated with each threshold of TSP except for TSP60. For one thousand hours per year in excess of TSP200 the relative risk for this group was 1.37 (C.I. 1.05, 180) (Table 2) (Mills, submitted 1990). Risk was also elevated for the respiratory cancers, although this finding was not statistically significant for any of the thresholds.

For OZ, the thresholds included 10, 12, 15, 20, and 25 pphm. Table 2 summarizes the relative risks for a 500 hour per year average annual increase above OZ10. The relative risk for respiratory cancer for OZ10 was 2.25 for five hundred hours per year in excess of this threshold which was of borderline statistical significance (C.I. 0.96-5.31). The results of the analysis of mean concentration of TSP and OZ were also elevated but were not statistically significant.

When risk of myocardial infarction was evaluated in relation to ambient TSP levels, there was a slight increase in risk associated with TSP60 which was of borderline statistical significance. This increase was observed in both the stratified analysis and the regression analysis. However, none of the other threshold levels were associated with increased risk nor was there increased risk associated with mean concentration of TSP.

Ambient levels of oxidants were not associated with altered risk of M.I. in this population either in regard to any threshold level of OZ or of mean concentration of OZ. For five hundred hours in excess of OZ10, the multivariate adjusted relative risk for M.I. was 1.06 (C.I. = 0.69-1.61) (Table 2).

The relationship between all natural cause mortality (1977-1986) and ambient levels of TSP and OZ was examined and no alterations in risk emerged either when various threshold levels of TSP and OZ were examined nor when mean concentration was examined. (Table 2). For one thousand hours in excess of TSP200 the relative risk for all natural cause mortality was 0.99; for five hundred hours in excess of OZ10 the relative risk was unity (Table 2).

#### **TSP AND OZ AS RELATED TO RESPIRATORY SYMPTOMS**

Incidence of definite symptoms of AOD and chronic bronchitis were statistically significantly ( $p < 0.05$ ) elevated for average annual hours in excess of 100, 150, and 200  $\text{mcg}/\text{m}^3$  and mean concentrations of TSP but not for 60  $\text{mcg}/\text{m}^3$ . For incidence of asthma, there was significantly elevated

risks only for average annual hours above thresholds of 150, and 200 mcg/m<sup>3</sup>. Table 2 shows the relative risk for 1000 hours per year in excess of TSP200 for AOD and chronic bronchitis. Neither mean concentration nor any of the thresholds of ozone were statistically significantly associated with cumulative incidence of any of the respiratory symptoms outcomes, though a trend association ( $p = 0.056$ ) was noted between OZ10 and cumulative incidence of asthma. The point estimate of relative risk for asthma was 1.40 (95% C.I. = 0.99-2.34). See Table 2.

## DISCUSSION

The pertinent results from this study indicate that risk of all malignant neoplasms among females, definite symptoms of AOD and chronic bronchitis as well as asthma are all significantly associated with ambient concentrations of TSP for thresholds of 100 mcg/m<sup>3</sup> and higher, and for asthma a threshold of 150 mcg/m<sup>3</sup> and higher. Moreover, there is suggestive evidence that risk of respiratory cancer, and asthma may be associated with elevated levels of ambient ozone at a threshold of 10 pphm.

Several considerations, however, need to be taken into account in interpreting these findings. Although the study has numerous strengths that have been lacking in previous studies including the fact that it is a prospective study involving only non-smokers who were geographically stable for a period of at least ten years prior to the beginning of follow-up, certain limitations in the study design should be noted.

Estimates of air pollution exposure used in this study were estimates of ambient concentrations only. Studying the associations between adverse health effects and ambient concentrations is useful, since ambient concentrations are monitored and air quality standards are based on them. Future analyses of these data, however, will attempt to model subjects exposure more accurately by use of adjustment factors obtained in other human exposure modeling studies. The lack of incorporation of such factors in the present analyses are likely to make statistically significant associations more difficult to demonstrate as long as they are not systematically biased due to an increase in uncontrolled variability (8).

Measurement error in cumulative ambient concentrations may have resulted from our use of

interpolations from fixed site monitoring stations. A validation study, which compared concentrations at monitoring stations with those interpolated by surrounding stations indicated a correlation of 0.83 for mean concentration of TSP and in excess of 0.80 for mean concentrations of ozone. (2, and Abbey submitted) Sensitivity analyses of these data were conducted which restricted individuals to those living within distances from monitoring stations regarded as having acceptable quality by EPA. The results of these sensitivity analyses indicate concurrence with the results described above (2, and Mills Submitted).

Another weakness in the present study is that the respiratory cancer analysis was based on only seventeen cases. In the future we plan to extend follow-up and to conduct a nested case-control study within the cohort with a larger number of respiratory cancer cases and an appropriate reference group.

It is difficult to explain the higher cancer incidence risk in females associated with TSP. Much smaller percentages of the females had been exposed to tobacco smoke and occupational fumes and dust. Only 14% of the females had a history of past smoking, compared to 36% of the males. There is some evidence that the increased risk of lung cancer associated with urban living is more apparent in non-smokers than smokers (9, 10, and 11). This is consistent with females' stronger relationship between TSP exposure and cancer incidence in this study.

Particulate matter in ambient air is known to contain substances which exhibit carcinogenic activity in experimental systems (12). The polycyclic aromatic hydrocarbons have received the most attention; several are known to be carcinogens in both animals and humans (13). A direct relationship between increasing exposure to TSP and increasing cancer incidence and mortality rates would therefore be expected.

Although the majority of studies attempting to evaluate the air pollution-cancer relationship have focused on lung cancer (e.g. 14), several studies have investigated relationships with cancer and at all sites and non-respiratory tract cancers. For example, Winkelstein and Kantor found that both stomach and prostate cancer mortality rates were higher in the area of Buffalo, New York, with higher TSP pollution than in the less polluted areas (15, 16). Other investigators noted significantly higher mortality rates for cancers of the stomach, esophagus, and bladder in more highly polluted areas of Nashville,

Tennessee than in less polluted areas (17). In the present study, large increases in risk of respiratory cancer were observed for elevated TSP ambient concentrations, yet increased risks for all malignant neoplasms were also observed, especially in females. These increased risks suggest that high ambient levels of TSP may have both local and systemic effects on cancer induction. Tobacco smoke exhibits similar effects. It greatly enhances the risk of tumors arising in the bronchial lining of the lung, which has a direct, intimate contact with the smoke, but also enhances the risk of cancers in the pancreas and bladder, which are exposed to carcinogenic metabolites of various tobacco constituents (18).

Only one case-control study of air pollution and lung cancer has been reported to date (19). In that study of white males, cases (n = 417) and controls (n = 752) were selected from residents of areas of high, medium, or low TSP levels (the maximum level was 200 mcg/m<sup>3</sup>). The authors reported a non-significant odds ratio of 1.26 for residence in the high pollution area. Despite these findings, the authors pointed out that there was increased lung cancer risk from smoking and occupational exposure if there was also long-term exposure to air pollution.

In this study, no association between ambient levels of TSP or OZ and definite myocardial infarction was found. We also evaluated other cardiovascular disease outcomes including definite coronary heart disease death and sudden death but observed no relationships between these outcomes and ambient concentrations of TSP or OZ.

Most previous studies of air pollution and cardiovascular disease have focused on the role of carbon monoxide (CO). There does seem to be good evidence that exposure to elevated levels of atmospheric CO enhances the onset of angina in persons with pre-existing cardiovascular disease (20) and that the case-fatality rate from myocardial infarction is higher in highly polluted areas during periods of relatively increased CO pollution (21). The number of our study subjects living close enough to monitoring stations to enable ambient CO estimates was too small to warrant analyses.

In the Nashville air pollution study, cardiovascular disease morbidity was associated with increasing levels of a soiling index although particulates measured by a high volume sampler showed an inverse association with cardiovascular morbidity among white males greater than 55 years of age. White

females, however, showed direct positive relationships with all pollutants measured in that study (22). Although it appears that data on social class and race were obtained, no adjustments were made for these factors nor were smoking habits evaluated. A subsequent report from the same study restricted the analysis to middle class participants only and reported a "consistent pattern of direct relationships of increasing cardiovascular disease mortality....for suspended particulate matter as measured by the soiling index." Again, however, it does not appear that the results were race or smoking history adjusted (23).

We did not detect any relationships between ambient levels of TSP or O<sub>3</sub> and all natural cause mortality in our population. Previous work has shown a relationship between ambient sulfates and particulates in relation to total mortality among 117 S.M.S.A. in the United States (24). These earlier results may have been due to concomitant exposure to high levels of sulfates or to other unmeasured variables which may have produced spurious results. It should be noted that such high levels of sulfates do not exist in California. However, our inability to detect elevated mortality rates at one thousand hours in excess of TSP200 is in general agreement with recent efforts to identify a "no effects observable level" which concludes that there are no effects on mortality below 150 mcg/m<sup>3</sup> mean concentration of TSP (25). Ostro, on the other hand, argues that there is not sufficient evidence to support a no observable effects level at 150 mcg/m<sup>3</sup> of British smoke, for example (26). It can be seen in our data (Figure 3) that there were insufficient numbers of study subjects above 150 mcg/m<sup>3</sup> of TSP mean concentration to adequately assess health effects at those levels.

By definition, incidence for the respiratory symptoms complexes excluded those individuals who had definite symptoms in 1977. These individuals may be the ones most susceptible to respiratory effects as a result of high levels of ambient concentrations of TSP and ozone. To assess this possibility, a respiratory symptoms severity score was developed for each of AOD, chronic bronchitis, and asthma (7). Analyses for TSP and ozone were repeated incorporating those individuals who had definite symptoms in 1977 and using multiple linear regression models to relate change in score 1977-1987 to pollutant thresholds and mean concentration. The results of these analyses are reported by Abbey



(Abbey, submitted) were in general concurrence with the incidence results described above with the following exceptions: Mean concentration of ozone (1977-1987) and the 1977-1987 average annual hours in excess of thresholds 10 pphm and 12 pphm of ozone showed statistically significant ( $p < 0.05$ ) associations with change in the asthma severity score. When change in symptoms score rather than incidence was used for chronic bronchitis, no statistical significance was detected for the threshold of 100  $\text{mcg}/\text{m}^3$  of TSP though statistical significance was still achieved for higher thresholds. These results suggest that asthmatics may be especially sensitive to continued elevated levels of ambient concentrations of ozone.

Although analyses of these health outcomes with  $\text{SO}_2$  have not yet been completed, it is unlikely that  $\text{SO}_2$  is confounding our results as average annual levels of  $\text{SO}_2$  in all of our study areas are below 25  $\text{mcg}/\text{m}^3$  which is low in comparison with other studies of the health effects of ambient air pollutants (27).

The findings of our study are consistent with those of the UCLA population studies of chronic obstructive pulmonary disease which were conducted on subjects in areas of high versus low oxidant air pollution of Southern California (28, 29). The UCLA studies failed to show significant associations of oxidant air pollution with incidence of respiratory symptoms, but did show statistically significant associations of oxidant air pollution with declines in lung function.

The general conclusion of a number of recent review articles is that elevated concentrations of total suspended particulates contribute to respiratory morbidity over and above the effects due to cigarette smoking (27, 30). Our findings relating elevated ambient levels of TSP to incidence of respiratory symptoms in non-smokers are consistent with this.

Results of our analyses pertaining to incidence of respiratory symptoms is in close agreement with previous reports on associations of TSP with prevalence of respiratory symptoms in this population (2). However, previous analyses of prevalence of definite AOD symptoms showed statistically significant associations with total oxidants whereas our current analyses failed to show any statistically significant associations between cumulative 10 year incidence of AOD and total oxidants/ozone. (3).

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**TABLE 1**  
**Definition of subcohorts of the AHSMOG population identified in 1977 and followed-up for various periods of time for various disease outcomes.**

<u>Cohort and Disease Endpoint</u>	<u>Questionnaire Data Obtained in:</u>	<u>Period of Follow-up</u>	<u>No. of Persons</u>	<u>Person-years</u>
Cancer and Myocardial Infarction Incidence Population	1976, 1977	1977-1982	6303	34,431
All Natural Cause Mortality Population	1976, 1977	1977-1986	6303	56,567
Respiratory Symptoms Population	1976, 1977, 1987	1977-1987	3914	_____ a.

a. Person-years were not calculated for the respiratory symptoms cohort since date of onset of symptoms was not ascertained on the questionnaire and, therefore, person-time analyses were not feasible.

**TABLE 2**  
**Relative risks for cancer, myocardial infarction and all natural**  
**cause mortality for exceedance frequencies above 200 ug/m<sup>3</sup> of TSP**  
**and above 10 pphm ozone.**

<u>Outcome</u>	<u>N</u>	<u>1000 Hours Above TSP200</u>	<u>500 Hours Above Oz 10</u>
All Malig. Neoplasms <sup>a</sup> in Males	115	0.96 (0.68-1.36)	1.09 (0.80-1.47)
All Malig. Neoplasms in Females	175	1.37 (1.05-1.80)	1.03 (0.81-1.32)
Respiratory Cancer	17	1.72 (0.81-3.65)	2.25 (0.96-5.31)
Definite <sup>b</sup> Myocardial Infarction	62	0.93 (0.57-1.51)	1.06 (0.69-1.61)
All Natural <sup>c</sup> Cause Mortality	845	0.99 (0.87-1.13)	1.00 (0.89-1.12)
AOD Definite <sup>d</sup> Symptoms	272	1.36 (1.11-1.85)	1.02 (0.85-1.29)
Bronchitis Definite <sup>e</sup> Symptoms	234	1.33 (1.07-1.81)	1.20 (0.97-1.52)
Asthma <sup>f</sup>	80	1.74 (1.11-2.92)	1.40 (0.99-2.34)

a. Variables included as covariates in the Cox models for cancer (besides age) include total years of past smoking and education attainment. Hazardous occupation was also included for males.

b. Variables included in the model for definite M.I. (besides age) include sex, education attainment, history of high blood pressure and Quetelet's Index.

c. Variables included in the model for mortality included (besides age) sex, education, total years of past smoking and presence of definite symptoms of AOD in 1977.

d. Variables included in the model for definite AOD symptoms include (besides age) education, sex, childhood colds, childhood AOD, possible symptoms in 1977, years smoked, years lived with a smoker and years worked with a smoker.

e. Variables included in the model for definite bronchitis symptoms included (besides age) education, sex, childhood colds, possible symptoms in 1977, years smoked and years lived with a smoker.

f. Variables included in the model for definite asthma included (besides age) education, sex, possible symptoms in 1977 and years worked with a smoker.

PERCENT OF POPULATION n = 6102

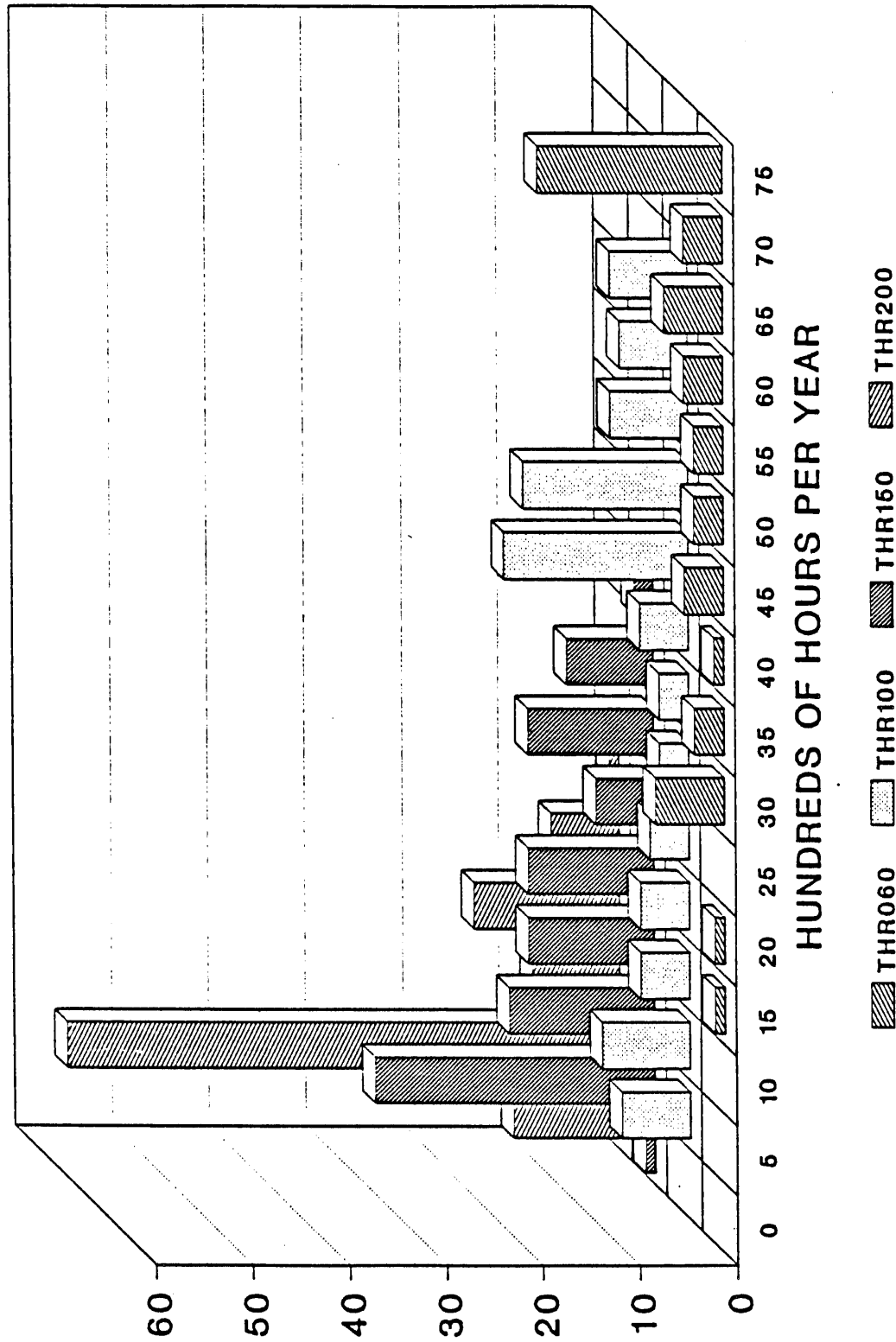


Figure 1. Distribution of hours in excess of various thresholds of total suspended particulates in the study population, 1973 - 1977.

PERCENT OF POPULATION n = 6058

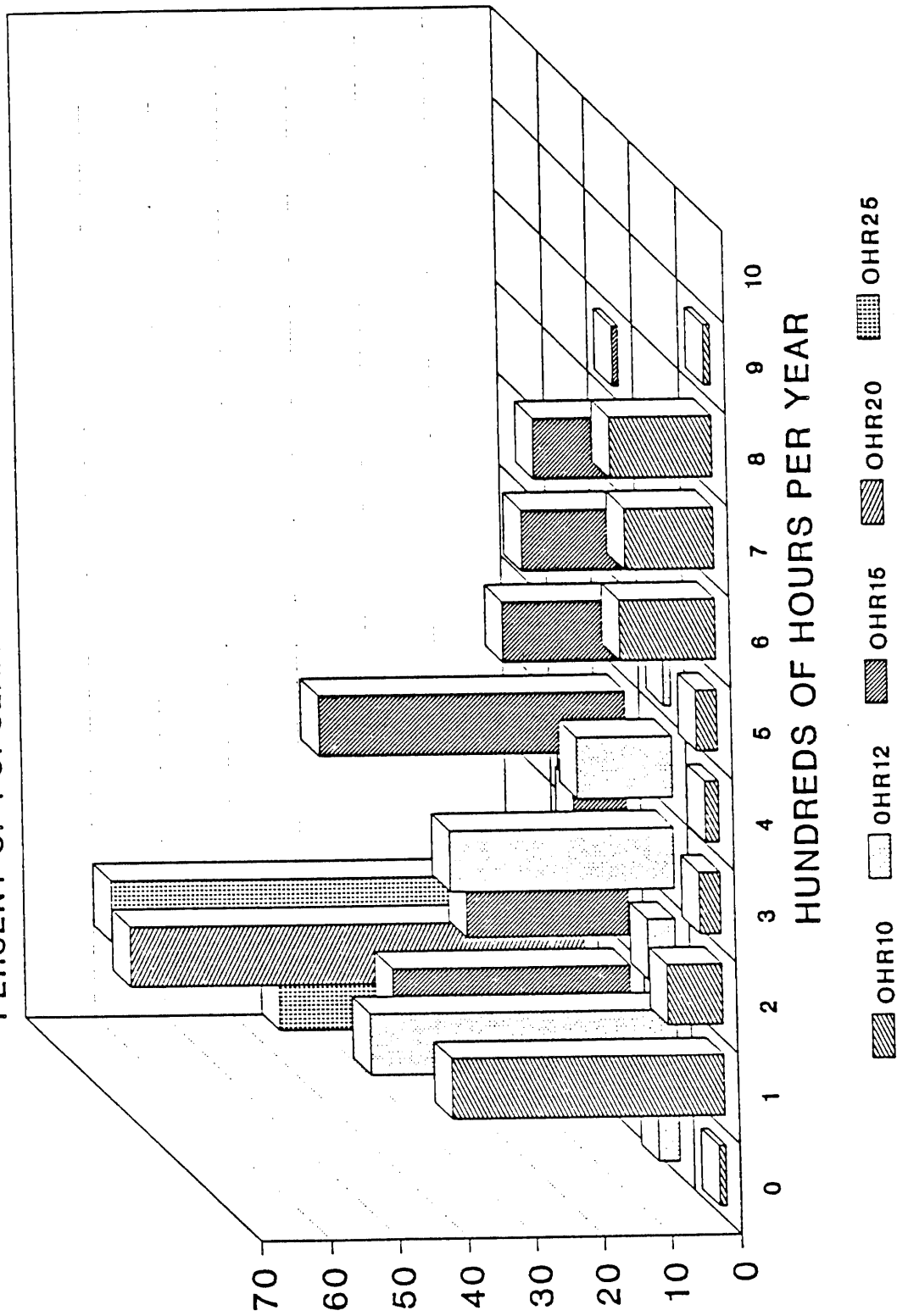


Figure 2. Distribution of hours in excess of various thresholds of ozone in the study population, 1973-1977.



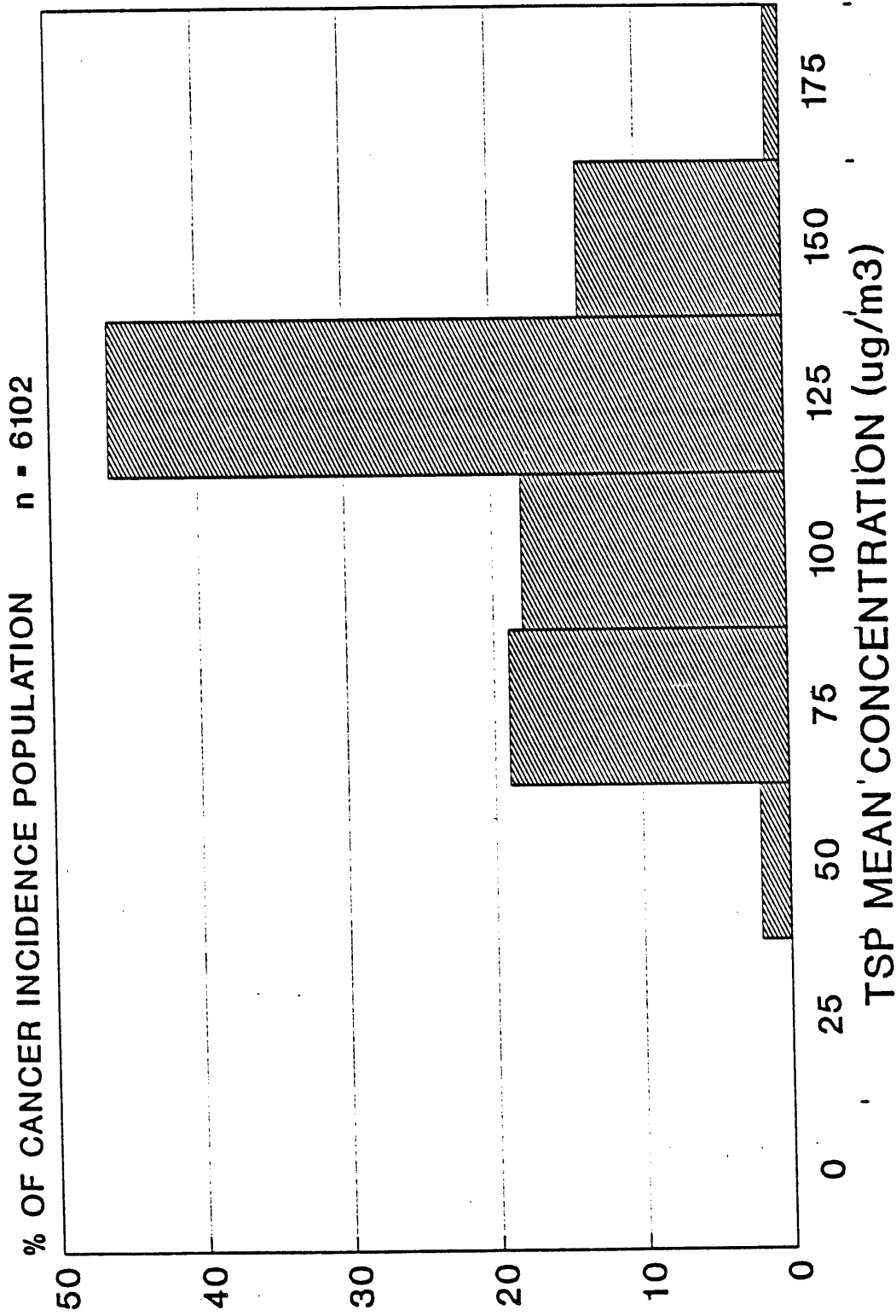


Figure 3. Distribution of mean concentration of total suspended particulates in the study population, 1973-1977.

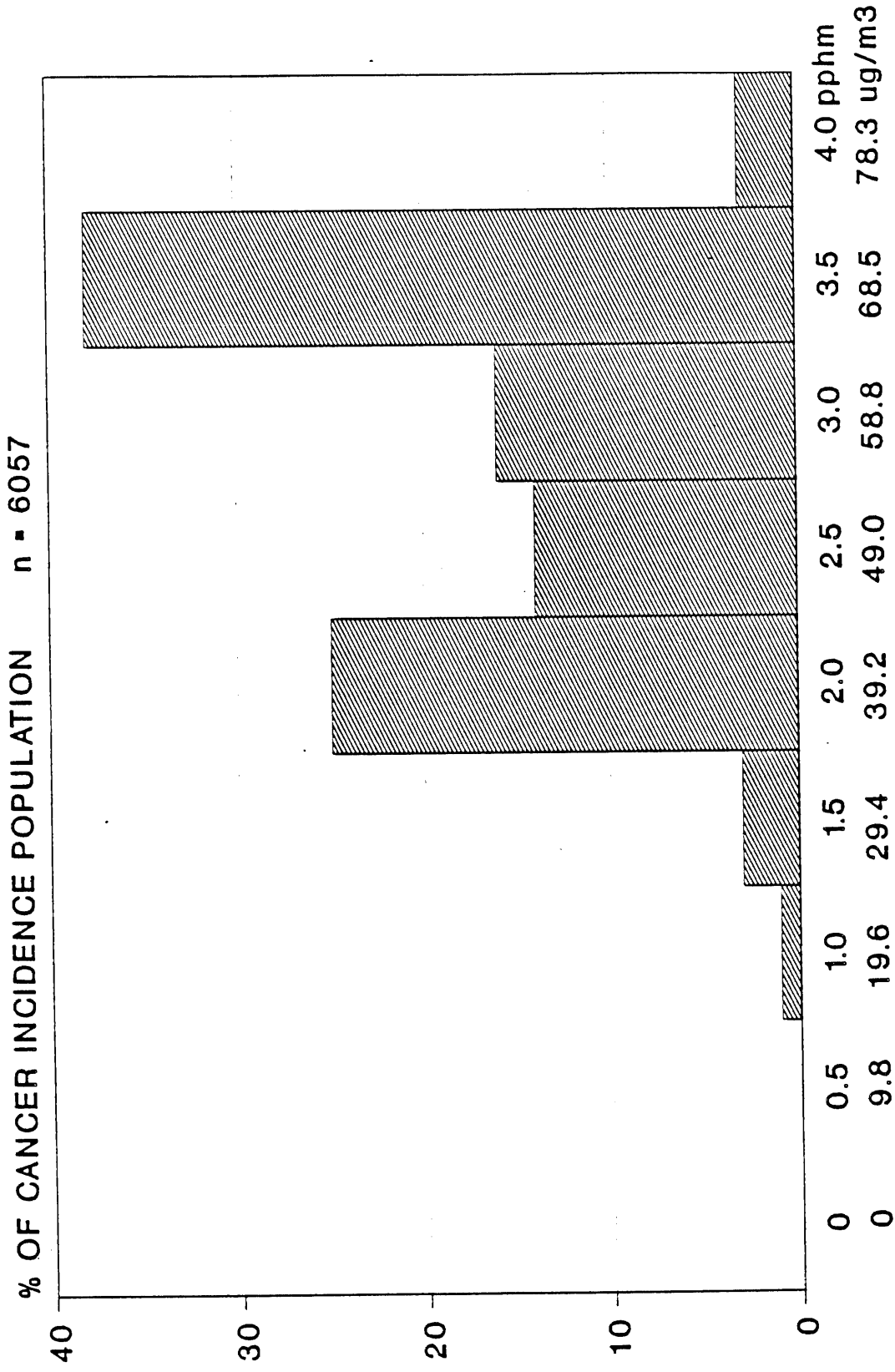


Figure 4. Distribution of mean concentration of ozone in the study population, 1973-1977.

**LONG TERM SULFUR DIOXIDE LEVELS AND ADVERSE HEALTH EFFECTS  
IN NON-SMOKING CALIFORNIA SEVENTH-DAY ADVENTISTS**

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## ABSTRACT

Long-term ambient concentrations of sulfur dioxide were evaluated in relation to several chronic disease outcomes in a cohort of approximately six thousand non-smoking California Seventh-day Adventists. The diseases of interest included symptoms of respiratory disease, cancer, myocardial infarction and all natural cause mortality. Sulfur dioxide levels were monitored between 1967 and 1987 throughout the state of California and chronic disease incidence in the cohort was monitored between 1977 and 1982 for the cancer and heart disease outcomes and between 1977 and 1987 for the respiratory disease and mortality outcomes. The analysis of the data included both a stratified and a multivariate Cox proportional hazards regression approach. After taking into account several disease specific confounding variables, no significant relations emerged between long-term sulfur dioxide levels and any of the disease outcomes which were analyzed.

## INTRODUCTION

A recent report by the National Academy of Sciences concluded that "current air pollution can cause acute and perhaps chronic health effects, particularly respiratory effects in the population of the United States" (1). However, valid and reproducible epidemiological studies of adverse health effects associated with ambient air pollution are difficult to conduct in most human populations due to the confounding effects of cigarette smoking and other variables. Several studies of air pollution and health have been completed using the Seventh-day Adventists population of California, however, a non-smoking population which experiences a wide degree of variation in exposure to various ambient air pollutants. For example, Hodgkin et al. reported a statistically significant fifteen per cent increase in definite symptoms of chronic obstructive pulmonary disease (termed airway obstructive disease (AOD) in this paper) in non-smoking Adventists residing in an area of high pollution (the South Coast Air Basin of California) compared to those residing in less heavily polluted areas of the state. This result persisted in a multivariate analysis which controlled for several confounders including age, sex, race, education, adverse occupational exposures and past smoking history (2). Euler demonstrated statistically significant increased prevalence of definite symptoms of AOD associated with both sulfur dioxide ( $\text{SO}_2$ ) and total suspended particulates (TSP) in this same population (3). A later study also demonstrated statistically significant elevated prevalence of definite AOD symptoms associated with total oxidants but not nitrogen dioxide (4). A multipollutant analysis conducted in this latter paper showed that  $\text{SO}_2$  failed to retain a significant association with AOD when

TSP was included as an exposure variable in the model.

These studies have been useful contributions in that they have demonstrated significant alterations in risk in a non-smoking population and have quantified that risk in reference to numbers of hours in excess of various thresholds of ambient air pollutants corresponding to state and national standards. However, they have been restricted to the analysis of the cross-sectional data then available in which respiratory symptoms data recorded by questionnaire at one point in time (1977) were correlated with ambient air pollutants levels during previous years. Longitudinal data are now available for this population for a six year period of follow-up (1977-82) during which time incident respiratory symptoms data, cancer incidence data and cardiovascular disease data were gathered. Mortality data are available for a ten year follow-up period (1977-1986). Additionally, incidence of respiratory symptoms has been ascertained for a ten year period (1977-1987) for those individuals still living in 1987. Recent papers have reported on associations of health effects ascertained from this longitudinal data and TSP and ozone. Analysis of long term cumulative levels of TSP and OZ indicated that risk of malignant neoplasms among females increased with increasing frequencies of all thresholds of TSP except the lowest one and those increased risks were highly statistically significant. For respiratory cancers increased risk was associated with only one threshold of OZ and this result was of borderline significance (5). Analysis of respiratory disease symptoms indicated statistically significant elevated risks for incidence of asthma, definite symptoms of airway obstructive disease (AOD) and chronic bronchitis with TSP in excess of all thresholds except the lowest one but not

for any thresholds of O<sub>3</sub>. A trend association was noted between the threshold of 10 pphm ozone and incidence of asthma (6). No associations were observed for all natural cause mortality or incidence of definite M.I. with either TSP or ozone ).

In this report we extend the results of the analysis of the longitudinal data to include results regarding ambient levels of SO<sub>2</sub> as they are related to airway obstructive disease, cancer, cardiovascular disease and all natural cause mortality.

## METHODS

This is a prospective epidemiological study involving approximately six thousand Seventh-day Adventists living in California in 1976 who were participants in the Adventist Health Study and who had resided within five miles of their current residence for at least ten years. By church proscription, Adventists do not smoke although some members of this cohort (36% males, 14% females) smoked prior to joining the church. In addition to completing a detailed lifestyle questionnaire in 1976, members of this cohort completed the NHLBI respiratory symptoms questionnaire in 1977. This 1977 questionnaire also elicited detailed lifetime residential histories which were used to construct air pollution profiles for study participants. Measures of ambient air pollutants including TSP, ozone, sulfur dioxide and sulfates in those areas of California inhabited by members of the cohort were provided by the California Air Resources Board for the period 1966-1977. Details of how these data were collected are described by Abbey (8, 9). Therefore, as of 1977, each member of the study cohort had been carefully characterized as regards lifestyle habits, residential history and ambient concentration of several air pollutants.



Between 1977 and 1982 the cohort was followed-up and monitored for newly diagnosed cancer and myocardial infarction. Details of the follow-up procedure have been described by Beeson (10). Mortality follow-up of the cohort has been completed through 1986. The analyses presented in this report concerns risk of cancer, myocardial infarction (1977-1982), and all natural cause mortality (1977-1986) as they were related to long term ambient levels of sulfur dioxide (SO<sub>2</sub>). Moreover, the NHLBI respiratory symptoms questionnaire was completed again in 1987 along with ascertainment of additional covariates by approximately 85% of the surviving members of the 1977 cohort. Results of the analysis of SO<sub>2</sub> as regards incidence of respiratory symptoms and change in severity of respiratory symptoms (1977-1987) are also presented in this report. The size and nature of the various sub-cohorts discussed in this report (which are not mutually exclusive) are summarized in Table 1.

### STATISTICAL ANALYSIS

Different statistical methods were used for the data on cancer and cardiovascular disease incidence and all natural cause mortality compared to the respiratory symptoms data due to differences in the covariates available and the nature of the outcome data. We first describe the statistical methods used for the data on incidence of cancer and cardiovascular disease and all natural cause mortality; then the statistical methods for the respiratory symptoms data.

#### Analyses for Cancer, Heart Disease and Mortality Data

Frequency distributions of SO<sub>2</sub> inside and outside SCAB were examined in order to create cutpoints for the tertile categories used in preliminary age and sex adjusted

stratified Mantel-Haenszel analysis. These distributions are graphically summarized in Figures 1 and 2. The cutpoint used in creating the lowest exposure category for both pollutants was taken to be that level experienced by 90% of the study population residing outside the SCAB. The middle and upper tertiles were then created by dichotomizing the remainder of the study population. After these tertiles were identified, age and sex adjusted relative risks and 95% confidence intervals were calculated for each level of SO<sub>2</sub> using the adaptation of the Mantel-Haenszel method for person-years data (REF). Trend p-values were also calculated to determine the significance of dose-response relationships in the data. These preliminary stratified analyses were conducted as a check on the results of the final more sophisticated multivariate models since they do not make any assumptions about linear or additive effects.

Cox proportional hazards regression models were constructed which incorporated, in addition to age and sex, several other covariates which were deemed potentially confounding. The terms included in the final models depended on the disease outcome of interest. Examples of additional covariates include total years of past smoking, educational attainment and exposure to passive smoke at home or work. The specific covariates included in each model are presented in the footnotes to the tables.

For both the stratified analysis and the multivariate analysis mean concentration of SO<sub>2</sub> (1973-1977) was used as the main exposure variable in relation to risk of disease during the follow-up period which commenced in April of 1977. As a check, however, the final Cox models were rerun using average annual concentration for the

time period 1966 through 1977 as the exposure variable and also 1973 through year of risk set. In addition to mean concentration of SO<sub>2</sub>, the threshold level of 4 pphm SO<sub>2</sub> was also analyzed since earlier work in this study has indicated a significant positive association between this level of SO<sub>2</sub> and prevalence of AOD (3).

In the Cox models, for each of the disease outcomes except all natural cause mortality, age was used as the time variable in the model since age is more closely related to risk of disease than time on study (11). However, since we have detected a substantial "Healthy Volunteer Effect" as regards mortality in this data set (10) for the mortality analysis we used time on study as the time variable in the Cox models and incorporated age (as of 4/1/77) as a covariate in the models.

As a check on the proportionality requirement of the Cox model, log-log plots were created and the hazard function was examined across strata of covariates. In no case was a violation of the proportional hazards assumption indicated by a cross-over in the hazard function.

#### Analyses for Respiratory Symptoms Data

Multiple logistic regression models were used for studying associations between cumulative incidence (1977-1987) of definite respiratory symptoms and long-term cumulative ambient concentrations of SO<sub>2</sub>. Individuals having definite symptoms in 1977 were excluded from analyses which used cumulative incidence as an outcome. Individuals having possible symptoms in 1977 were included in such analyses and a covariate was included to this effect. Another set of statistical analyses used change in a respiratory symptoms severity score as the outcome variable. All individuals were

included in these analyses, with a positive value of change in score indicating an increase in severity of symptoms and a negative value indicating a decrease in severity of symptoms. The 1977 symptoms severity score was used as a covariate in these analyses. Multiple linear regression models were used for studying associations between change in respiratory symptoms severity score and long-term cumulative ambient concentrations of SO<sub>2</sub>.

Multivariate models were used in order to adjust for a number of covariates simultaneously. The candidate covariates for the multivariate models are described in detail by Abbey (6) along with their descriptive statistics for the cohort. The covariates include demographic variables, past and passive smoking variables, occupational exposures to air pollutants, and previous respiratory symptoms. The demographic variables were forced into all regression models and included gender, age, and years of education as of April 1, 1977. The past and passive smoking variables included years smoked in the past, years lived with a smoker, and years worked with a smoker. The exposures to occupational air pollutants included years of dust exposure at work, and years of fume exposure at work. In addition to total years (lifetime through 1987) of exposure to cigarette smoke and occupational air pollutants, exposure was measured in periods prior to 1977, and between 1977 and 1987. In addition to this, whether or not a person currently worked or lived with a smoker in 1987 and whether or not a person was currently exposed to dust or fumes at work was recorded. None of those individuals included in the study reported currently smoking in 1977 or since 1977.

Previous respiratory symptoms included frequency of childhood colds, whether

or not the individual had experienced definite symptoms of airway obstructive disease before the age of 16, and whether or not the individual had possible respiratory symptoms in 1977 or for the change in respiratory symptoms severity analyses a 1977 respiratory symptoms severity score.

In order to ensure adjustment for demographic characteristics, three demographic variables - gender, age, and education - were forced into all multivariate analyses. Education was used as the best surrogate in this population for socioeconomic level. As some Adventists work for the church for "missionary" wages, we felt that education was a better indicator of socioeconomic level for this population than income.

Because of the large number of covariates available, stepwise selection procedures were used to determine a final model by selecting from among the secondary variables (all those other than the demographic factors), those variables which were most strongly and statistically significantly related to the outcome variable. These stepwise procedures were stopped when additional candidate variables entering the model failed to achieve statistical significance at the 0.05 level. For the variables which represented cumulative exposures over time, such as passive smoking and SO<sub>2</sub>, three forms were allowed to compete with each other for entry; these forms corresponded to lifetime through 1977, exposures from 1977 through 1987, and lifetime through 1987. For SO<sub>2</sub>, "lifetime" was replaced with cumulations since 1973 which was used as a surrogate for cumulations since 1966. It was felt that interpolations since 1973 were of better quality since the number of monitoring stations greatly increased

in 1973. The final models were checked by replacing cumulations since 1973 with cumulations since 1966. In no case were significant changes in results noted.

#### **DEFINITION OF CANCER, HEART DISEASE AND MORTALITY OUTCOMES**

Associations with ambient levels of SO<sub>2</sub> were made with six disease outcome categories including all malignant neoplasms (ICDO, 140-200) in males, all malignant neoplasms in females, respiratory cancer (ICDO, 160-165), definite myocardial infarction and all natural cause mortality (ICDO 000-799). For the first four of these outcomes, incident events were considered for the time period 4/1/77 through 12/31/82. Since mortality ascertainment of the cohort had been extended through 1986 at the time this analysis was initiated, the follow-up period for the analysis of all natural cause mortality included 4/1/77 through 12/31/86.

#### **DEFINITION OF RESPIRATORY SYMPTOMS OUTCOMES**

Computer algorithms were used to classify individuals as having chronic bronchitis, asthma, or emphysema. These computer algorithms were based on 21 respiratory symptoms questions from the standard NHLBI questionnaire. Hodgkin (2) lists the respiratory symptoms questions which were used and gives the percentage of individuals having each symptom; they are explicitly defined by Abbey (6).

The computer algorithms classified individuals as having "definite" chronic bronchitis, "definite" emphysema, or "definite" asthma. Individuals meeting the criteria for one of these three diagnoses were classified as having "definite" airway obstructive disease (AOD). To be classified as having "definite" chronic bronchitis, individuals must have had symptoms of cough and/or sputum production on most days, for at least

three months per year, for two years or more. For a diagnosis of "definite" asthma, individuals must have been told by their physician that they had asthma, as well as having a history of wheezing. For emphysema, subjects must have been told by their physician that they had emphysema, as well as having shortness of breath when walking or exercising. Individuals not meeting the criteria for "definite" symptoms for a respiratory symptoms complex, but having some respiratory symptoms associated with that complex, were classified as "possible". In addition to a classification of "none", "possible", or "definite" for each respiratory symptoms complex, a severity score was developed for each respiratory symptoms complex as well as for overall AOD to reflect the relative severity of the symptoms. The detailed definitions of these scores are given in Abbey (6).

The computer algorithms were used to classify and score the individual's respiratory symptoms complexes as ascertained by questionnaire in 1977 and again in 1987. Since there were an insufficient number of cases of emphysema to warrant disease specific analyses for this outcome, we restricted analyses to the three outcomes - AOD, chronic bronchitis, and asthma. Cumulative incidence for each of these outcomes was defined as having definite symptoms in 1987 but not having definite symptoms in 1977.

## RESULTS

### Cancer, Myocardial Infarction and All Natural Cause Mortality

For the incident disease events, approximately 25,000 person-years of follow-up occurred between 1977 and 1982. Numbers of cases were as follows: All malignant

neoplasms in males and females were 89 and 136 respectively; 14 respiratory cancers; 50 cases of definite myocardial infarction and 639 deaths from all natural causes, 1977-1986 (in approximately 41,000 person years of observation).

The association between mean concentration of SO<sub>2</sub> (1973-1977) and the six disease outcomes are presented in Table 2. For all malignant neoplasms in both males and females the coefficients are positive. They are also positive for definite myocardial infarction and all natural cause mortality but the absolute value of the coefficients for the latter two disease outcomes are an order of magnitude smaller than for the cancer outcomes. None of the coefficients approach statistical significance. For respiratory cancers, and the respiratory symptoms outcomes, the regression coefficients are actually negative in sign. These results were unchanged when the exposure period included 1966-1977 and are compatible with the results obtained in the Mantel-Haenszel stratified analysis. As a check on the results obtained using mean concentration of SO<sub>2</sub>, the threshold level of 4 pphm of SO<sub>2</sub> was also examined since earlier results have suggested that ambient concentrations in excess of this level of SO<sub>2</sub> were associated with an increased prevalence of definite symptoms of AOD in this population (3). Again, none of the beta coefficients approach statistical significance.

## DISCUSSION

SO<sub>2</sub> was not as widely monitored as TSP and ozone in our study areas. This resulted in losing approximately 24% of the person years from the cancer and heart disease incidence data and 28% of individuals from the respiratory symptoms analyses due to individuals living greater than the maximum interpolation distance of 50



kilometers from a station monitoring SO<sub>2</sub>. The EPA has suggested categories of distances from stations within which the concentrations monitored at the stations may be considered representative (12). The quality ratings for SO<sub>2</sub> are the same as for TSP and are described by Abbey (9). Quality ratings were incorporated into the interpolations to reflect these distance categories. The final statistical models for each outcome were rerun, restricting interpolations to those which could be considered representative or moderately representative, less than 6 miles or 9.6 kilometers. Results concurred with those described above. This restriction, however, resulted in reducing the number of individuals available for analyses by another 50%.

A separate study of the accuracy of interpolating ambient concentrations from monitoring stations described in detail by Abbey (9) indicated no statistical difference between cumulative 2 year concentration of SO<sub>2</sub> at monitoring stations and those interpolated from the three nearest monitoring stations. The correlation between interpolated and monitored values was 0.63.

The negative results reported in this study relating long term ambient levels of SO<sub>2</sub> to adverse health effects in humans should be considered within the context of the geographic area within which the study was conducted. Although the study location included three large metropolitan areas of California and some of these areas experienced relatively high levels of TSP and O<sub>3</sub> during this time period, ambient levels of SO<sub>2</sub> were relatively low.

#### Levels of Sulfur Dioxide in the Areas Under Study

Within the South Coast Air Basin (SCAB) where two-thirds of the population

resided for example, average mean concentration of SO<sub>2</sub> for the time period 1973-1977 was only 1.2 pphm (0.012 ppm) while outside SCAB average mean concentration of SO<sub>2</sub> was only 0.30 pphm. In contrast, in more polluted areas of metropolitan New York, during 1971-1972, SO<sub>2</sub> levels varied from 0.067 to 0.162 ppm (13). These low levels may have 1) resulted in no adverse health effects as we have reported or 2) adverse health effects of a magnitude which were too small to detect given the size of the study population. Previous studies of this same study population during the same time period have, however, noted increased prevalence of AOD associated with 4 pphm of SO<sub>2</sub> (3). In a later multipollutant analysis, however, Euler (4) noted that the association of SO<sub>2</sub> and AOD was no longer statistically significant when TSP was added as an exposure variable in the model. Because of this, and the fact that our current analyses use incidence of AOD as ascertained by prospective follow-up, we tend to attach more credence to the current findings of no association.

Ware et al summarized the evidence for health effects (primarily AOD) of long term exposure to SO<sub>2</sub> in 1981 (14). The lowest level of SO<sub>2</sub> reviewed in that report corresponded to 1 pphm which is higher than the levels evaluated in this study. In that review Ware noted that at 1 pphm the only adverse health effect was increased frequency of acute lower respiratory disease. These results were obtained in a cross-sectional study in two communities in the southeastern United States (15).

Since the time that Ware's review was published we have located an additional eight studies (16-22) which have evaluated ambient SO<sub>2</sub> levels as related to AOD. These studies are summarized in Table 4 which demonstrates that, when levels of SO<sub>2</sub>

were reported that they were much higher than the levels reported in this study.

Our negative results regarding SO<sub>2</sub> levels and all natural cause mortality are in agreement with a recent analysis of mortality and air pollution in London which concluded that, after taking into account the influence of particulates "the evidence for an independent relation between SO<sub>2</sub> and mortality is weak (23). There are data, however, which indicate that there are short term effects of SO<sub>2</sub> on total mortality and that these effects are independent of particulates (24).

Our negative findings regarding SO<sub>2</sub> levels and the cancer outcomes is also consistent with most previous studies which have addressed this issue. Only one correlational study which evaluated SO<sub>2</sub> levels as high as 111 mcg/m<sup>3</sup> found an association with respiratory cancer that was statistically significant (R = 0.37) (25). Again these levels are higher than levels experienced in metropolitan areas of California, 1973-1977.

Relatively few investigations of air pollution and cardiovascular disease have been conducted and those which have been done were primarily concerned with ambient levels of carbon monoxide as it relates to heart disease (26). There is some limited evidence that there may be an association between SO<sub>2</sub> and cardiovascular deaths and between sulfate levels and exacerbation of heart disease in the elderly (27) although no evidence exists in our data to support any association between ambient SO<sub>2</sub> and the incidence of definite myocardial infarction.

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**TABLE 1**  
**Definition of Subcohorts of the AHSMOG Population Identified in 1977 and Followed-Up for Various Periods of Time for Various Disease Outcomes.**

<u>Cohort and Disease Endpoint</u>	<u>Questionnaire Data Obtained in:</u>	<u>Period of Follow-up</u>	<u>No. of Persons</u>	<u>Person-years</u>
Cancer and Myocardial Infarction Incidence Population	1976, 1977	1977-1982	6303	34,431
All Natural Cause Mortality Population	1976, 1977	1977-1986	6303	56,567
Respiratory Symptoms Population	1976, 1977, 1987	1977-1987	3914	_____ a.

a. Person-years were not calculated for the respiratory symptoms cohort since PRECISE DATE of onset of symptoms could not be ascertained and, therefore, person-time analyses were not feasible.



**TABLE 2**  
**Cox Proportional Hazards Regression Analysis of Mean Concentration Of SO<sub>2</sub>**  
**(1973-1977) and Several Disease Outcomes In the AHSMOG Incidence Population.**

<u>Disease Outcome</u>	<u>N</u>	<u>β</u>	<u>S.E. (B)</u>	<u>Z</u>
All Malignant Neoplasms - Males <sup>1</sup>	89	0.0001375	0.0002107	0.65
All Malignant Neoplasms - Females	136	0.0001325	0.0001641	0.81
Respiratory Cancer	14	-0.0003634	0.0005467	-0.66
Definite M.I. <sup>2</sup>	50	0.0000216	0.0002746	0.08
All Natural Cause Mortality <sup>3</sup> (1977-1986)	639	0.0000013	0.0000760	0.02
Definite Symptoms of AOD <sup>4</sup>	202	-0.05664	0.1421	-0.399
Definite Symptoms of Chronic Bronchitis <sup>5</sup>	176	-0.63269	0.3956	-1.60
Asthma <sup>6</sup>	61	-0.37554	0.2653	-1.42

1. Terms included in the model were age, sex, education, total years smoked and exposure to occupational air pollutants (males only). Years lived or worked with a smoker were allowed to compete for entry but failed to enter.
2. Terms included in the model were age, sex, education, hx of blood pressure, Quetelets index and total years smoked. Hx of diabetes, breathlessness index and exercise index were allowed to compete for entry but failed to enter.
3. Terms included in the model were age, sex, education and total years smoked. Definite AOD and years lived and worked with a smoker were allowed to compete for entry but failed to enter.
4. Terms included in the model were age, sex, education, total years smoked, whether or not had possible symptoms of AOD in 1977, years of dust exposure through 1987, and frequency of childhood colds.
5. Terms included in the model were age, sex, education, total years smoked, whether or not had possible symptoms of chronic bronchitis in 1977, frequency of childhood colds, years of dust exposure at work through 1987, years lived with a smoker through 1977.
6. Terms included in the model were age, sex, education, whether or not had possible symptoms of asthma in 1977, years worked with a smoker through 1987.

TABLE 3  
RECENT EPIDEMIOLOGIC STUDIES OF AIR POLLUTION AND AIRWAYS OBSTRUCTIVE DISEASE (AOD)

Source, year	Type of Study Type of Data Geographic Loc.	Sample (Sex, age, race)	Exposure Variable (& levels of high exposure)	A.O.D. Outcome	Effect measure estimate and C.I.	Smoking and Occup?	Passive Smoking?	Indoor Pollut?	Major Findings
Ware et al. (1986)	Six Sites study: 3 year, longitudinal 1974-1977	10,106 white, Preadolescent school children	TSP TSO <sub>4</sub> SO <sub>2</sub>	Frequency of: cough bronchitis lower res- piratory illness	Regression Coefficient	Yes	Yes	No	Frequencies of cough, bronchitis, and lower respiratory illness during the one year period prior to the second annual examination were significantly associated with TSP and TSO <sub>4</sub> concentrations during the same period.
Pengelly et al (1984)	Cross- sectional prevalence study in Hamilton, OH 1978	3553 school children	TSP	Frequency of: Mother cough, father cough, chest illness in siblings, respiratory hospital admit as infant	Prevalence	No	No	No	Prevalence of morbidity highest in high air pollution areas of the city. Not statistical tests conducted.
Whittle- more and Korn (1980)	Panel study of asthmatics in L.A. 1972- 74.	16 panels of asthmatics	TSP, RSP SO <sub>x</sub> , NO <sub>x</sub> SO <sub>2</sub> , OX	Asthma attack	regression coefficient	Yes	No	No	The panelists tended to have increased attacks on days with high oxidant and particulate pollution.
Aubrey et al. (1979)	Cross- sectional study in Montreal, CAN	300 men: women, 45- 64 years of age	TSP SO <sub>2</sub>	Cough Phlegm Breath- lessness		Yes	No	No	When inter city differences in age and smoking were taken into account, no differences in health status could be shown.

Source, year	Type of Study Type of Data Geographic Loc.	Sample (Sex, age, race)	Exposure Variable (& levels of high exposure)	A.O.D. Outcome	Effect measure estimate and C.I.	Smoking and Occup?	Passive Smoking?	Indoor Pollut?	Major Findings
Bates & Sizto, 1987	Correlation study in Southern Ontario, 1974-1983.	79 Acute care hospitals serving 5.9 million people	O <sub>3</sub> (68 ppb) NO <sub>3</sub> (5.21 pphm) SO <sub>2</sub> (3.97 pphm) COH (9.48 mo.1) Aerosol sulfates	1) % deviation in total resp. admissions 2) total resp. admissions excluding asthma 3) asthma admissions, all ages 4) asthma admissions, age 0-14 yrs.	Pearson correlation coefficients	No	No	No	Significant correlations exist between O <sub>3</sub> , SO <sub>4</sub> , SO <sub>2</sub> , temperature and % deviation from mean respiratory admissions. Stepwise multiple regressions indicate that in summer SO <sub>4</sub> and temperature account for about 5% of the variance in respiratory or asthma admissions.
Schenker 1983	Cross-sectional study in western PA, 1974-1979	5557 adult women randomly selected from area telephone directories	SO <sub>2</sub> (99 mcg/m <sup>3</sup> )	1) Chronic cough 2) Chronic phlegm 3) Wheeze most days or nights, 4) Dyspnea, grade 3	Relative odds (95% C.I.)	Yes	Yes	No	Risk of "wheeze most days or nights" in non-smokers residing in the high and medium pollution areas was 1.58 and 1.26 (p=0.02) respectively, relative to residents in a low pollution area. Among those who resided in the same place for at least 5 years, the relative risks increased to 1.95 and 1.40 respectively (p<0.01).
Mazumda r 1983	Correlation study in Allegheny Co. 1972-1977	Population of Allegheny Co.	SO <sub>2</sub> COH	No. of urgent/ emergency admissions for respiratory disease.	% premature health effects"	No	No	No	One of the monitoring stations' data showed a significant (p<0.05) association between COH and respiratory disease morbidity.

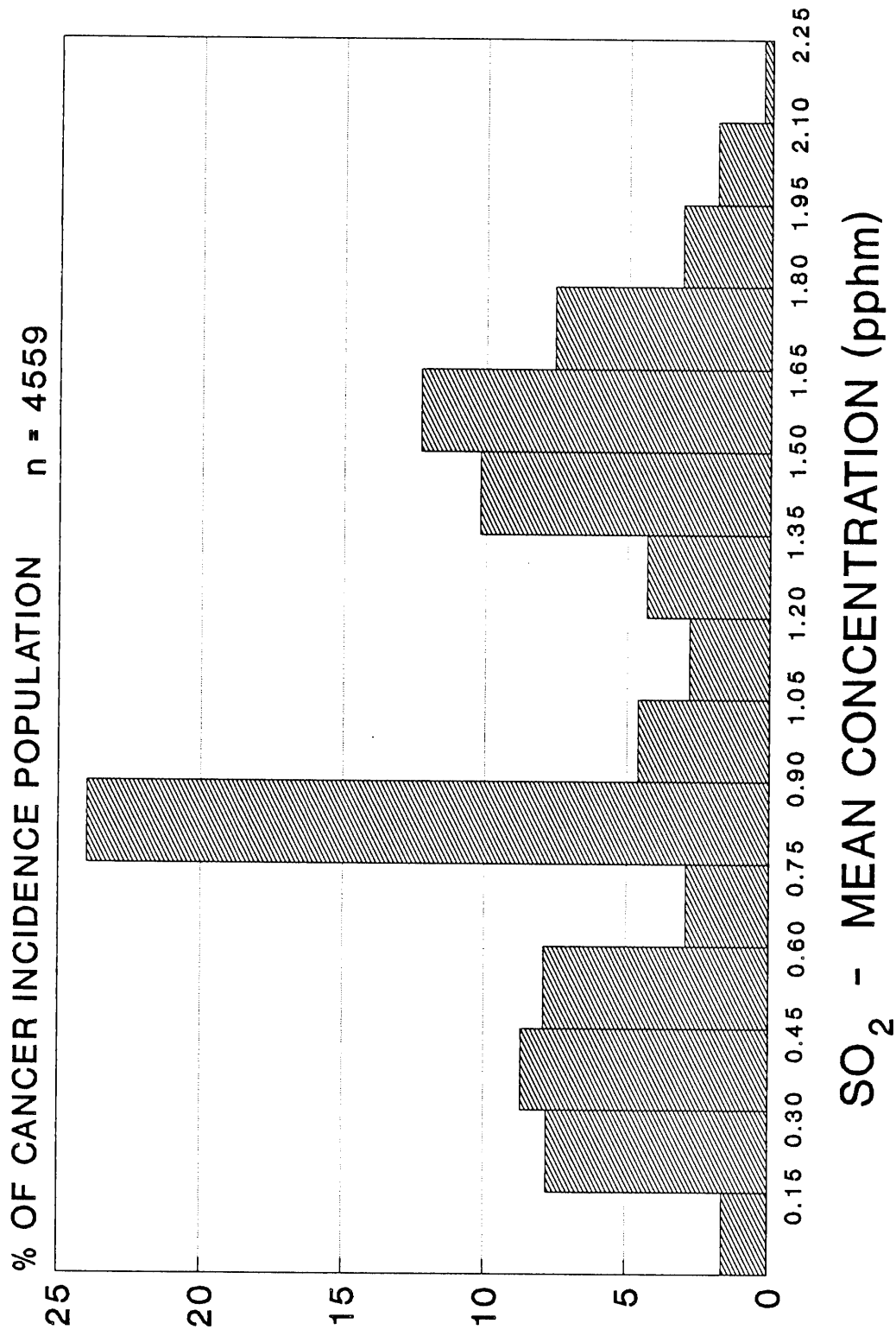
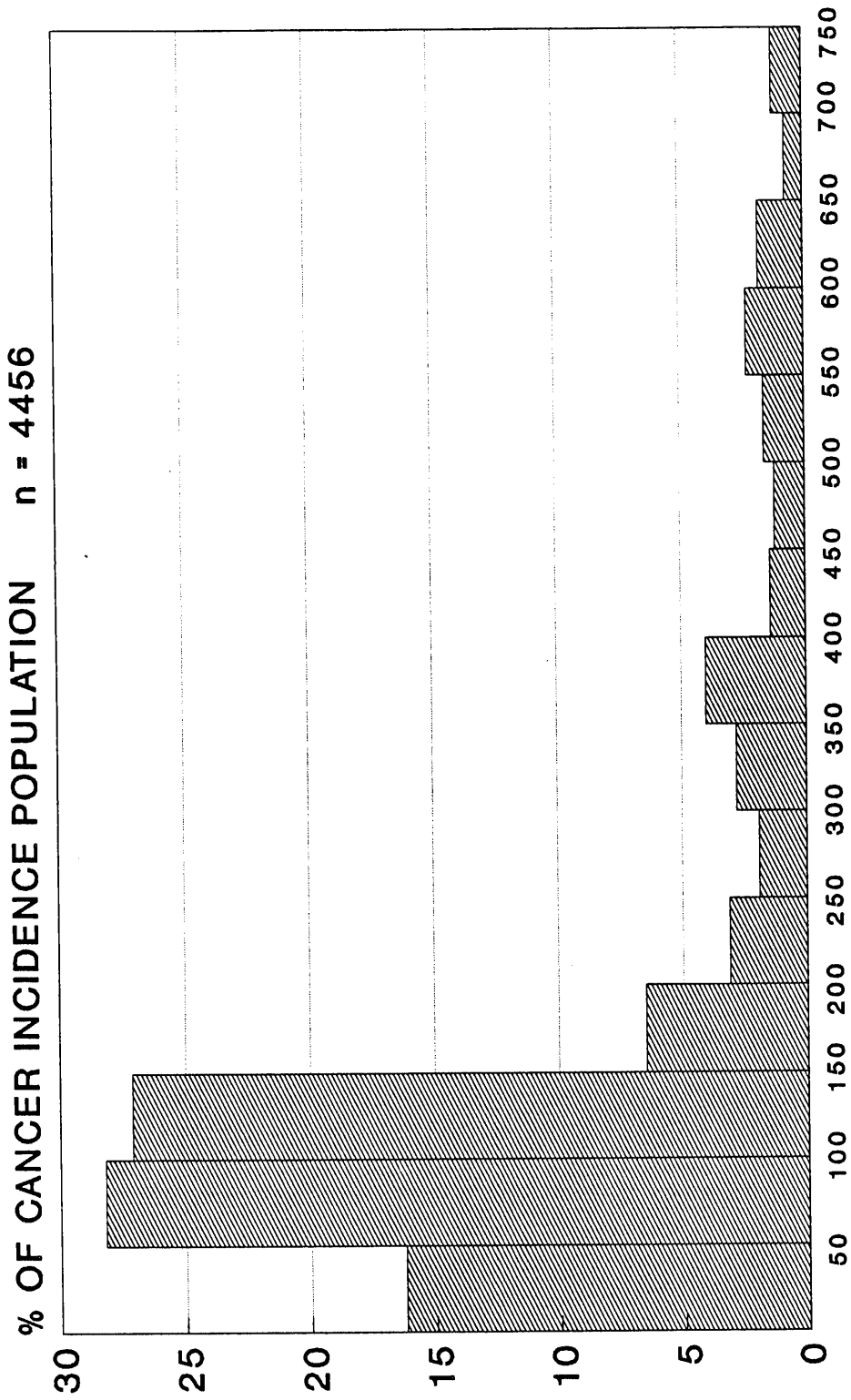


Figure 1. Distribution of sulfur dioxide in the study population, 1973-1977.



**SO<sub>2</sub> - HOURS IN EXCESS OF 4 pphm**

Figure 2. Distribution of sulfur dioxide  
in the study population, 1973-1977.

