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Incidence of Respiratory Symptoms and Chronic Disease in a Non-Smoking Population as a Function of Long-Term Cumulative Exposure to Ambient Air Pollutants (Adventist Health Study of Smog Follow-Up Study)

Volume 1: Final Report

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
AIR RESOURCES BOARD
Research Division

Incidence of Respiratory Symptoms and Chronic Disease in a Non-Smoking Population as a Function of Long-Term Cumulative Exposure to Ambient Air Pollutants

(Adventist Health Study of Smog Follow-Up Study)

Volume 1: Final Report
(See Volume 2 for Appendix of Papers)

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This report summarizes all the methods and results of the Adventist Health Study of Smog Follow-up Study, work performed between December 30, 1986 and August, 1993 under ARB contracts A6-128-33 "Incidence of Respiratory Symptoms and Chronic Diseases in a Non-Smoking Population as a Function of Long-Term Cumulative Exposure to Ambient Air Pollutants;" A833-057 "Incidence of Respiratory Symptoms and Chronic Diseases in a Non-smoking Population as a Function of Long-Term Cumulative Exposure to Ambient Air Pollutants;" and A933-160, "Incidence of Respiratory Symptoms and Chronic Disease in a Non-Smoking Population as a Function of Long-Term Cumulative Exposure to Ambient Air Pollutants."

This report is also the Final Report on contract A933-160.

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.

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ABSTRACT

A cohort of 6340 non-smoking California Seventh-day Adventists have been followed since 1977 for: incidence of cancer and myocardial infarction through 1982, development of definite symptoms of, and increasing severity of, airway obstructive disease, chronic bronchitis, and asthma through 1987, and all natural cause mortality through 1987. Cumulative ambient concentrations of seven pollutants have been estimated for study participants from 1967 to 1987 by interpolating monthly statistics from statewide air monitoring stations to zip codes of residence and work location. Pollutants studied included total suspended particulates (TSP); inhalable particulates less than 10 microns in diameter, estimated from regressions on TSP; fine particulates less than 2.5 microns in diameter (PM2.5), estimated from airport visibility data; suspended sulfates; ozone; sulfur dioxide (SO_2); and nitrogen dioxide (NO_2).

Multivariate statistical models which adjusted for several covariates showed no statistically significant associations between any of the diseases studied and NO_2 or SO_2. None of the pollutants studied showed statistically significant associations with all natural cause mortality or incidence of all malignant neoplasms in males. Statistically significant associations were observed between elevated ambient concentrations of one or more particulate pollutants and each of the other diseases. Ozone was significantly associated with increasing severity of asthma, and development of asthma in males.

Cross Reference Table for Published Papers Which Address Associations Between Specific Air Pollutants and Diseases

Disease Outcome		TSP	Ozone	SO_2	NO_2	SO_4	PM10	PM2.5	Visibility
DEVELOPMENT OF:	AOD	5,8	5,8	8	10	9	15	17	17
	Chronic Bronchitis	5,8	5,8	8	10	9	15	17	17
	Asthma	5,8	5,8,13	8	10	9	15	17	17
INCREASING SEVERITY OF SYMPTOMS OF:	AOD	8	8	8	10	9	15	17	17
	Chronic Bronchitis	8	8	8	10	9	15	17	17
	Asthma	8	8	8	10	9	15	17	17
INCIDENCE OF ALL MALIGNANT NEOPLASMS IN:	Males	5,7	5,7	11	10	Not Done(1)	16	12	(2)
	Females	5,7	5,7	11	10	Not Done(1)	16	12	(2)
RESPIRATORY CANCER INCIDENCE		5,7	5,7	11	10	Not Done(1)	16	Not Done(1)	Not Done(1)
ALL NATURAL CAUSE MORTALITY		5,7	5,7	11	10	11	16	12	(2)
INCIDENCE OF M.I.		5,7	5,7	11	10	11	16	Not Done(1)	Not Done(1)

(1) Not Done = No statistical test of association made due to small number of incident cases; or in case of SO_4 insufficient lag time between exposure and incidence ascertainment.

(2) Not a published paper.

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1. Hodgkin JE, Abbey DE, Euler G, Magie AR. COPD prevalence in nonsmokers in high and low photochemical air pollution areas. Chest December, 1984:86;830-838 . . . . . P 1-1

2. Euler GL, Abbey DE, Magie AR, Hodgkin JE. Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. Arch Environ Health, July/August, 1987:42(4);213-222 . . . . . P 2-1

3. Euler GL, Abbey DE, Hodgkin JE, Magie AR. Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total oxidants and nitrogen dioxide in California Seventh-Day Adventist residents. Arch Environ Health, July/August, 1988:43(4);279-285 . . . . . P 3-1

4. Abbey DE, Euler GL, Moore JK, Petersen F, Hodgkin JE, and Magie AR. Applications of a method for setting air quality standards based on epidemiological data. JAPCA, April, 1989:39(4);437-445 . . . . . P 4-1

5. Abbey DE, Mills PK, Petersen F, Beeson WL. Long term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-day Adventists. Environmental Health Perspectives, August, 1991:94;43-50 . . . . . P 5-1

6. Abbey DE, Moore J, Petersen F, Beeson WL. Estimating cumulative ambient concentrations of air pollutants: Description and precision of methods used for an epidemiological study. Arch Environ Health, 1991:46(5);281-287 . . . . . P 6-1

7. Mills PK, Abbey DE, Beeson WL, Petersen F. Ambient air pollution and cancer Arch Environ Health, 1991:46(5);271-280 . . . . . P 7-1

8. Abbey DE, Petersen FF, Mills PK, Beeson WL. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a non-smoking population. Arch of Environ Health. 1993:48(1);33-46 . . . . . P 8-1

9. Abbey DE, Petersen FF, Mills PK, Kittle L. Chronic respiratory disease associated with long term ambient concentrations of sulfates and other air pollutants. J of Exposure Anal and Environ Epidemiol. 1993:3(S1);99-115 . . . . . P 9-1

10. Abbey DE, Colome, SD, Mills PK, Burchette R, Beeson WL, Tian Y. Chronic disease associated with long term concentrations of nitrogen dioxide. J of Exposure Anal and Environ Epidemiol. 1993:3(2);181-202 . . . . . P10-1

Chapter 1

Introduction

§ 1.1 Introduction/Overview

The purpose of the study was to assess the health effects of long-term ambient concentrations of air pollutants on a non-smoking population in California. The study enrolled 6,340 non-smoking California Seventh-day Adventists in 1977 and followed them through 1987, for ascertainment of chronic respiratory diseases as well as cancer and myocardial infarction incidence.

In this chapter we will first outline the contents of this report and then briefly review a previous study on this cohort. Chapter 2 describes the methods used to generate estimates of ambient air pollutant concentrations for study participants. It contains a description of the statistics used to represent long-term cumulative concentrations, the methods used to interpolate estimates from fixed site monitoring stations to the residence and work locations of study participants and the methods used to adjust ambient concentrations to reflect time spent indoors by study participants. Two of the ambient air pollutants - inhalable particulates less than 10 microns in diameter, PM10, and fine particulates less than 2.5 microns in diameter, PM2.5 were estimated indirectly. The methods of indirect estimation are outlined briefly in Chapter 2 and detailed in Appendices D and E.

Chapter 3 describes the epidemiological and statistical methods used in the study. These epidemiological methods include the 1977 and 1987 survey methods, the inclusion/exclusion criteria for the study, the methods of ascertainment for cancer incidence and myocardial infarction incidence, the definition and methods of ascertainment for all natural cause mortality and the definitions of the respiratory symptoms complexes. A description of a reliability study for self-reported asthma is given. The statistical methods include a description of the statistical models and covariates used to relate ambient concentrations of pollutants to health outcomes, as well as the stepwise selection procedures used to select covariates for statistical models.

Chapters 4 through 10 summarize the health effects results by pollutant. Chapter 4 summarizes the results for total suspended particulates (TSP), chapter 5 for total oxidants/ozones (OZ), chapter 6 for sulfur-dioxide (SO_2), chapter 7 for suspended sulfates (SO_4), chapter 8 for nitrogen dioxide (NO_2), chapter 9 for inhalable particulates less than 10 microns in diameter (PM10), chapter 10 for fine particulates less than 2.5 microns in diameter (PM2.5). Chapter 11 describes multipollutant analyses which were conducted to determine which pollutants are most statistically significantly related with each disease outcome and which relationships may be due to surrogate relationships with other pollutants. We will henceforth use the terms significant or significantly to mean statistically significant at the .05 level with a 2-tailed test. Chapter 12 gives an overall summary of the study and discussion of results, and may be read without the other chapters, for those readers interested in a quick overview of the study findings.

Appendix A contains the questionnaires used on the cohort in 1977 and 1987 and gives the response percentages for each category of each question for those who completed the questionnaire in 1987. Appendix B gives a detailed description of the respiratory symptoms algorithms used to define health outcomes as well as reliability checks conducted for self-reporting of respiratory symptoms. Appendix C details the regression adjustment methods that were used for NO_2 based on a personal exposure study to NO_2 in southern California. Appendix D details the indirect estimation methods that were used for estimating PM2.5 from airport visibility data. Appendix E details the indirect estimation methods used for estimating PM10 from site and seasonal specific regression equations based on TSP. Appendix F contains ancillary tables and figures that are not included in the appendix of papers described below. Appendix G contains details of the methods used to interpolate concentrations from fixed site monitoring stations to zip codes of home and work location for study participants.

Also included is a separate appendix of papers from the study which have been published or submitted for publication. These papers contain detailed results and discussions of the results with respect to other published studies, and describe the statistical, epidemiological, and air pollution estimation methods in detail. Some tables and most figures contained in these papers are referred to by paper number and are not duplicated in the text. Tables in the text which are duplicated in published papers have the published paper number and table number in that paper in italics following the table number, so that the reader may refer to that paper for further detail or discussion of results. A cross reference table on page vi of this report is useful for finding which papers deal with a specific pollutant and disease outcome.

§ 1.2 Overview of Previous AHSMOG Study

An initial phase of this study, called the AHSMOG Study, analyzed the prevalence of definite symptoms of chronic obstructive pulmonary disease (COPD) as ascertained by questionnaire on the cohort in 1977, with respect to long-term ambient concentrations of total suspended particulates (TSP), total oxidants/ozone (OZ), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2). The papers published from this phase of the study are papers 1 through 4 in the appendix of papers. Henceforth, we will refer to papers in the appendix of papers by paper number without reference to the appendix and papers. The reader will be referred to this appendix of papers for pollutant specific tables and figures. COPD was later renamed Airway Obstructive Disease (AOD), though the definition remained the same, (see chapter 3, section 6) and is referred to as AOD in papers 4 through 17.

Paper 1 conducts a geographic analysis - comparing individuals who had resided for the previous 10 years within the South Coast Air Basin, to those who had resided the previous 10 years outside the South Coast Air Basin with respect to prevalence of definite symptoms of COPD. The relative risk prevalence of "definite" COPD was 15% higher in the South Coast Air Basin ($p = 0.03$) after adjusting for sex, age, race, education, occupational exposure and past smoking history. Past smokers had a risk estimate 22% higher than never smokers ($p = 0.01$). Multivariate analyses, adjusting for these factors, showed a significant effect of air

pollution on the prevalence of "definite" COPD which univariate analyses failed to demonstrate.

Paper 2 analyzed prevalence of definite COPD symptoms in 1977 using estimated concentrations of total suspended particulates and SO_2 for study participants. Estimated time per year in excess of different cutoffs were calculated for study participants. The cutoffs used for SO_2 were 2, 4, 8, and 14 pphm; those for TSP were 60, 100, 150, and 200 $\mu g/m^3$. Significant associations with definite COPD symptoms were found in multivariate analyses for: SO_2 concentrations above 4 pphm, ($p = 0.03$), relative risk 1.18 for 500 hours-per-year increase in ambient concentrations; and TSP concentrations above 100 $\mu g/m^3$. A relative risk prevalence of 1.22 was seen for definite COPD symptoms as associated with 1,750 hours increase in ambient concentrations above 200 $\mu g/m_3$ ($p < 0.00001$). Paper 1 also contains descriptive characteristics of the cohort, including the 1977 prevalence rates for each specific respiratory symptom, comparison of demographic distributions of the cohort with California, and average ambient pollutant levels for each of the three air basins - South Coast, San Diego and San Francisco.

Paper 3 found significant associations with relative risk prevalence of COPD symptoms and ambient concentrations of total oxidants/ozone (OZ) above 10 pphm ($p < .0004$, relative risk of 1.20 for an increase of 750 hours-per-year). COPD symptoms were not associated with relatively low NO_2 ambient concentrations in this population. A multipollutant analysis of TSP, SO_2, OZ, and NO_2 indicated that only TSP concentrations showed statistical significance. This paper concluded that ambient concentrations of TSP were more strongly associated with COPD symptoms than the other measured ambient concentrations or was the best single surrogate representing the mix of ambient pollutants present. Paper 4 is a methods paper describing the exceedance frequency statistics used and methods of interpolation to study participants residence and work place zip codes.

The statistical methods underlying the analyses for the 1977 results, as well as present analyses pertaining to development of symptoms, are outlined in Paper 4. Paper 4 contains a correlation matrix of all exceedance frequencies for the various cutoffs of each of the pollutants: OZ, NO_2, SO_2, and TSP.

The present report studies primarily development of new cases of chronic respiratory symptoms between 1977 and 1987 in contrast to prevalence of symptoms in 1977. Development of chronic bronchitis symptoms and asthma as well as overall AOD are studied as well as incidence of cancer and myocardial infarction and all natural cause natural cause mortality. The present analyses also found significant relationships of TSP and ozone with development of symptoms and showed no statistical significant effects of NO_2 as before. Unlike the analyses of 1977 prevalence of COPD, no statistically significant associations with SO_2 were found to be associated with development of COPD symptoms. Since the 1977 findings failed to sustain statistical significance of SO_2 in multipollutant analyses, it is possible that the SO_2 relationship with COPD prevalence observed in the 1977 reports were due to a surrogate relationship with TSP.

Chapter 2

Methods Used to Generate Estimates of Ambient Air Pollution Concentrations

§ 2.1 Indices, Time Periods Pollutants and Cutoffs for Cumulative Ambient Concentrations.

In this chapter we will describe and assess the precision of methods used to generate estimates of ambient air pollution concentrations for study participants. Two different types of monthly indices to characterize long-term ambient cumulative concentrations considered relevant to health effects were used. The first type of index, exceedance frequency, was used to represent the number of hours during which an ambient concentration exceeded a cutoff. It was calculated at each monitoring station on a monthly basis by counting the number of hourly values, for gaseous pollutants, or the number of 24 hour periods during which concentrations of particulate pollutants exceeded the specified cutoffs. For gaseous pollutants, the exceedance frequency for the month was calculated by computing the percentage of hours during which the cutoff was exceeded and then multiplying this percentage by the number of hours in the month. For particulate pollutants the number of 24 hour monitoring periods during which concentrations exceeded a cutoff was counted for each month. This number was then multiplied by the ratio (days in month per number of monitoring periods with data in month) and finally multiplied by 24 to convert the exceedance frequency to hours for ease of comparison with exceedance frequencies for gaseous pollutants. Note that these algorithms automatically adjusted for monitoring periods during which data were missing, and the adjustment assumed that these periods had the same distribution of concentrations as the periods for which complete data were available.

The second type of index used is called excess concentration. "Excess concentration function" was defined for each pollutant and cutoff as the concentration minus the cutoff if this difference was positive, and zero otherwise. Excess concentration during a month was the sum of the excess concentration function during all the month's monitoring periods. Excess concentrations were adjusted for missing data by the same rules used to adjust exceedance frequencies. The units for excess concentrations of gaseous pollutants were parts per hundred million-hours (pphm-h). Excess concentrations statistics for particulate pollutants were also expressed in terms of hours to facilitate comparison with gaseous pollutants, i.e., μg-h/m^3. The air pollution indices also included monthly mean concentrations, which could alternatively be defined as the excess concentrations above a zero cutoff divided by the number of hours in the month. Table 2.1 gives the cutoffs used for each pollutant. In general cutoffs were selected above and below state and federal standards so that health effects in relationship to these standards could be addressed.

Ambient pollutant indices were accumulated over different time periods before being used in statistical analyses. The first time period was 1966 through March 1977. The first mailing

and enrollment of the cohort took place in April of 1977. Because of the spareness of monitoring stations during the earlier years of this time period a surrogate time period 1973 through March 1977 was used for most analyses though key analyses were repeated using the longer time period. The second mailing of the questionnaire took place in April of 1987; thus the next time period used was April 1977 through March 1987. A third time period, 1973 through March 1987 was also used. In addition to these fixed time periods time dependent cumulations were also conducted to the earliest of date of death, date lost to follow-up and date health outcome ascertainment ceased. For mortality analyses the date ascertainment ceased was December 1986. For cancer and myocardial infarction incidence the date ascertainment ceased was December 31, 1982. These later time dependant accumulations were used in addition to the fixed time period accumulations for mortality and incidence analyses respectively. When using the time dependent accumulations in health outcome analyses, time dependent Cox proportional hazards regression models were used. In these models the risk of each member of the cohort is recalculated at each month an incident event occurs. This is called a risk set. For each risk set accumulations were recalculated for each member of the cohort through the earliest of: date of death, date lost to follow-up, (date of incidence for incidence outcomes), date of risk set.

§ 2.2 Interpolation Methods

This section describes the methods for interpolating ambient air pollution indices from fixed site monitoring stations to zip code centroids of residence and work location for study participants. These methods were used for all pollutants except PM2.5. The methods used for PM2.5 are described in a subsequent section. Appendix G gives further details for the interpolation methods.

To be used for interpolation to a zip code centroid, a monitoring station must have had a distance within 50 km (31.25 miles) of the zip code centroid and have been on the same side of any topographical or meteorological obstructions to air flow. A topographical obstruction was considered to be such if it rose more than 250 meters above the surrounding terrain. Meteorological air flow barriers were determined by CARB staff, (Abbey, 1989).

A station must also have "sufficiently complete data." Sufficiently complete data was defined to be at least 10 months of representative data for one or more pollutants in each of three or more years (in actual imputations this criteria was sometimes relaxed). For particulate pollutants which are monitored routinely for a 24 hour period, every sixth day, representative data was defined to be at least four 24 hour values in a month except for February where at least three were required. For gaseous pollutants which are monitored hourly, for a station to be representative it must have had at least 75% of the hourly values for the month. Those station months that had less data for a pollutant were considered to have missing data for that month and were not used for interpolation for that 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 at most three of the nearest stations that satisfied the conditions set forth below were included in an interpolation. The statistics used in the interpolation were weighted by $1/R^2$, where R was the distance from the station to the zip code centroid.

The EPA has suggested categories of distances from stations within which the concentrations monitored at the stations may be considered representative. These categories vary with the pollutant. Stations in distance categories A and B of a point were respectively considered representative and moderately representative of concentrations at the point. More distant stations within 50 km of the point were placed in category C. We assigned each interpolation a quality rating equal to the distance category of the nearest station. The distance categories for the quality ratings for each pollutant are given in Table 2.2.

A maximum of three stations was 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.

If the work location was more than 5 mi (8 km) from home, separate monthly interpolations were used for work and home locations. We assumed that individuals were at their work location from 8 A.M. to 5 P.M. Monday through Friday, except for federal holidays. There were hourly data for gaseous pollutants - ozone, NO_2, SO_2; therefore, the exceedance frequencies and excess concentrations for the home location could be calculated separately from those of the work location. Separate statistics for the month were calculated for particulate pollutants - TSP, PM10, SO_2, which were monitored for 24 hour periods, for the home and work locations. A weighted average of the home location and work location statistics was computed; assumed numbers of working and nonworking hours in a month were used for weighting. If information on an individual's work location was unavailable 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 California or in areas within California that were not within 50 km of a monitoring station. Such locations within California were examined manually by CARB staff who were knowledgeable about air pollution patterns in the state. Locations affected by pollution transport from nearby polluted areas were assigned the ambient concentration of the nearby polluted area and a quality rating of H, which denoted that the concentration had been "assigned" and was probably an upper limit to the true ambient concentration. Assignment of these quality codes enabled us to later exclude individuals who had too much "assigned data." Locations in low-pollution rural areas not affected by transport were assigned zero background exposures and a quality rating of I.

Values for months during which data were missing 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 nonmissing data. These imputed values were assigned separate quality codes so that individuals with too much missing data could be excluded from health effects analyses.

Exposures were coded as "possibly high" or "low" for locations outside California and were coded according to whether the individual resided for that month within 50 km of a city indicated by EPA to have an annual average exposure in excess of 60 $\mu g/m^3$ for TSP, 14 pphm for sulfur dioxide, or 12 pphm ozone. We considered months with values coded as "possibly high" to be missing because there were insufficient data available to assign a quantitative value. Months with values coded as "low" were counted as zero ambient concentrations in excess of all cutoff points, and a special quality code was assigned.

We coded months as missing for those individuals who had no fixed location during a month or who did not report a residence for the month. In the statistical analyses in which cumulative concentrations were used, 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 for whom we had actual data for fewer than 80% of the months were excluded from all analyses for all pollutants. Thus, the imputation procedures for missing values described above contributed data to the analyses only for individuals with 20% or fewer of their monthly values were missing. After applying this exclusion criteria the percentage of person months with imputed values due to missing data was small - for example less than 1% for TSP and ozone, less than 4% for NO_2.

§ 2.3 Precision of Interpolation

This section describes the assessment of precision of interpolation for all of the pollutants except PM2.5. For PM2.5 no interpolation methods were used. The precision of the interpolation methods was assessed by interpolating to monitoring stations from surrounding monitoring stations and cumulating over a two year period 1985 and 1986. Cumulated actual monitored ambient concentrations statistics at the stations were then compared to those interpolated from surrounding monitoring stations. Comparison of the resultant two year cumulations was achieved by paired t-test, correlation coefficients and regressions of actual on interpolated values. A table summarizing the correlation coefficients for the 2 year mean ambient concentration for each pollutant studied is given in Table 2.3. The detailed comparisons for TSP and ozone are shown in Table 1 of Paper 6; for SO_4, Table 1 of Paper 9; for NO_2, Table 1 of Paper 10; for SO_2, Table 1, Appendix F.

For PM10 a two step estimation process was used since PM10 was first estimated from TSP using regression equations as described below. These indirectly estimated values of PM10 at monitoring stations were then interpolated to other monitoring stations for assessment of precision. Assessment of the precision with which PM10 concentrations were estimated is discussed in section 2.6. For PM2.5, estimates were based on airport visibility measures and no interpolation schemes were used as described below.

§ 2.4 Indoor Adjustment Factors for all Pollutants Except NO_2

Adjustment factors were derived from Winer et al. (1989), to adjust ambient concentrations of pollutants for the time that study subjects remained indoors. The average time spent indoors was ascertained by season in 1977 and 1987. The adjustment factors for each pollutant are given in Table 2.2. These adjustment factors were applied to indoor hours, and adjusted mean concentrations were formed. Adjustments were not made to exceedance frequency statistics because no indoor/outdoor studies of these statistics have been made and we have no data on individual study participants on which hours of each day for the past twenty years they were outdoors. If there was disagreement between the time spent indoors, as reported in the 1977 questionnaire and 1987 questionnaire, we assumed that individuals changed habits at the time of retirement or, if not retired, at the midpoint during the time period. Adjustments were made only back to 1973 to avoid extrapolating 1977 reported habits too far back in time.

§ 2.5 Modeling Adjustment Factors for NO_2

For NO_2 a regression modelling procedure was used to "adjust" estimated ambient NO_2 concentrations for study participants so that indoor sources based on housing and lifestyle characteristics would be included. A regression estimation procedure was used to adjust ambient concentration estimates for the 3,914 Adventist Health and Smog Study (AHSMOG) study participants of respiratory symptoms cohort who completed the 1977 and 1987 questionnaires using data collected on building characteristics and individual activity patterns in 1987. These data, plus additional personal and ambient NO_2 exposure data, were collected on a sample of approximately 650 subjects from Los Angeles and Orange Counties (Spengler, et al, 1992). The data on the 650 subjects will be called GRI data since it was funded by the Gas Research Institute. The regression estimation equations were formed for this sample of 650 subjects and then applied to the AHSMOG cohort. The exposure data on the 650 subjects involved two consecutive 24 hour samples for each of the subjects on randomly selected days during the years 1987 and 1988. Outdoor ambient monitors and bedroom micro environmental monitors were placed in each study participant's home and were set to sample over the 48-hour period of personal monitoring. The NO_2 monitors were passive diffusion badges which enabled estimation of average concentration of NO_2 during each of the 24 hour measuring periods and for the 48-hour sampling duration. Study participants kept activity diaries and the household characteristics were reported on a questionnaire. Stepwise multiple regression procedures were used to select the best candidate predictor variables from the large pool of possible candidate variable common to both the GRI and AHSMOG Studies. Exhibit 7, Appendix C, compares the distributions for these variables between the GRI and AHSMOG populations. Note that we are not concerned with similarity of distributions but that the GRI data set spans the values of the AHSMOG data set so that the regression estimation procedures are not extrapolating.

The details of forming the multiple regression estimation equations are given in Paper 10. Three separate multiple regression prediction models were constructed: the first for individuals living in homes without gas ranges; the second for individuals living in homes with

gas ranges for the heating season; and a third model for individuals living in homes with gas ranges for the non-heating season. The three regression models are shown in Tables 3, 4, and 5 of paper 10. The variables used in the regression models which were characteristics of indoor environments were first multiplied by the fraction of time an individual reported spending indoors on the average. Outdoor ambient concentrations were multiplied by the fraction of time an individual reported spending outdoors on the average.

To assess how well the regression equations estimate personal exposure, the technique of split halves regression was used. To use this technique all 650 subjects were randomly divided into two groups of equal size. Regression equations were formed using the data from one group and then tested by applying them to the other group. These regressions were formed for the three separate groups - individuals without gas ranges, individuals with gas ranges sampled during non-heating months, and individuals with gas ranges sampled during heating months. The overall correlation across all three groups of predicted with observed values was 0.79 ($R^2 = 0.63$).

The final regression equations however, were based on all subjects. There is no way of knowing how well the equations predict actual personal exposure for AHSMOG study subjects. Nevertheless, this procedure of adjusting ambient concentration should be better than using only unadjusted ambient concentrations of NO_2. In order to partially evaluate the generalizability of the regression models to individuals at low as well as high ambient concentrations of NO_2, scatterplots of the residuals from regression models versus ambient concentration of NO_2 were made. These plots showed equal scatter of the residuals across all levels of ambient concentration. The plots are shown in Figures 1 and 2 of Appendix C.

The regression equations derived from the GRI data predicted 24 hour mean concentrations of NO_2 whereas for the AHSMOG study subjects it is necessary to predict monthly means, as the finest level at which data is available for the cohort is monthly data. Even though 24 hour ambient NO_2 concentrations in the prediction equations were multiplied by values of other variables in the models such as average fraction of time per month spent indoors, the values of these other variables are constant over a month for AHSMOG study subjects. Therefore, the average monthly ambient concentrations and average monthly values of variables can be substituted in the regression equations to predict average monthly adjusted concentration. The number of months per year AHSMOG study subjects heated their homes was available but not which months, thus in applying the season specific regression models to the AHSMOG cohort the heating season was defined by taking the number of months centered on January 15 if the number of months during which an individual used home heating was odd. It was centered on February 1 if the number of months home heating reported was even.

Since monthly data on ambient concentrations and monthly historical data on household characteristics and activity patterns were available for AHSMOG study participants, separate regression equations were used for each month for each individual study participant for the time period 1977 to 1987. If individuals had moved during this time period, data were not collected on previous places of residence. Thus the monthly ambient mean concentrations could only be

adjusted for the time period during which the individual lived in their 1987 residence. If individuals had not lived 80% of the months between 1977 and 1987 in their 1987 residence, they were excluded from calculations of adjusted mean concentration. This resulted in the loss of 1,630 individuals from the cohort of 3,914 individuals. The distribution of adjusted mean concentrations for 1977 through 1987 for those individuals for whom it could be calculated is shown in Figure 6 of Paper 10. Further details of the computer algorithms used to apply regression equations the AHSMOG cohort to produce estimates of NO_2 concentration are given in Appendix C.

§ 2.6 Indirect Estimation of PM10

This section outlines how indirect estimates of PM10 were formed using monitored TSP. Full details on the estimation methods are given in Appendix E, and a somewhat condensed version in the Methods section of Paper 15.

Because PM10 was not monitored on a consistent state-wide basis prior to 1985, an indirect method for estimating PM10 was necessary. Two alternative indirect methods were considered. The first method was to estimate PM10 from daily airport visibility data available for ten airports throughout California for the years 1966 through 1986. The second method was to estimate PM10 from TSP. TSP were monitored on a state-wide basis in a consistent manner from 1973 through 1987. Some stations began monitoring PM10 as early as 1982 and an increasing number of simultaneous observations of PM10 and TSP occurred after that date.

Using this paired PM_{10}/TSP data, the two alternative indirect estimation methods were compared for each of 17 site and, where necessary, seasonal specific data sets for stations in the vicinity of the ten airports. The R^2 for estimating PM10 from TSP was in every case higher than that for estimating PM10 from the visibility data as measured by the visibility estimation coefficient, β, see Table 1 of Appendix E. The average R^2 over the 17 data sets was 0.746 for estimating PM10 from TSP and 0.491 for estimating PM10 from visibility. Based on this comparison, it was decided to estimate PM10 from TSP.

In order to increase the precision of the final regression estimation equations the geographic areas were redefined, and the years extended to through 1989 in order to include additional simultaneous measurements of PM10 and TSP. The data set was also expanded to include geographic areas away from the vicinity of the 10 airports, since airport visibility data was no longer needed. Ninety-five stations throughout California had some paired PM10/TSP data available between the years 1982 and 1989. Stations used for regression estimation purposes were limited to the 70 of the 95 stations that had at least two paired data points from every calendar month (see Tables 4a and 4b of Appendix E). This was done to avoid a possible seasonal bias in the regression estimation equations. These 70 stations were grouped into 38 geographical areas in consultation with California Air Resources Board (CARB) staff with expertise and experience in fine particulate estimation and measurement. Particulate source characteristics, topographical and meteorological considerations were considered in forming the

geographical areas so they were expected to be as homogeneous as possible with respect to relationships between PM10 and TSP concentrations.

Regression estimation equations were formed for each individual station with sufficient paired data, as well as for geographic areas. For final PM10 estimation purposes individual station regressions, where available, were used in preference to regressions based on groups of stations. Two seasonal statewide regression equations and one nonseasonal statewide regression (never used) were also formed. These were used for certain areas of the state which lacked adequate paired PM10/TSP data to form their own regression equation. These efforts yielded 130 specific regression equations which were used to form indirect estimates of PM10, see Table 8a, Appendix E. The assignment of TSP stations to the 130 regression equations is given in Table 8b, Appendix E.

In order to evaluate the precision of the regression estimation equations, the separate regression sets were broken into their contributing stations. Individual stations sets were excluded only where two or more stations had been pooled to form a regression equation for a particular city and had not been used alone to form any regression set. The statewide regression equations were also excluded. This left 109 area and season specific regression equations containing nonredundant data points which were used for evaluation purposes. The number of data points upon which these regression equations were based ranged from 30 to 614 with a total of 14,314 data points. The R^2 for these regression estimation equations ranged from 0.61 to 0.94. The overall R^2, estimated by the split halves technique was 0.87. This technique is used to obtain an unbiased estimate of R^2 (Myers, 1990). A simple random sample of half of the data was used to form regression equations that were then used to generate predicted values for the other half; and these predicted values were correlated with actual values.

TSP stations which had been used to estimate cumulative ambient concentrations of TSP for AHSMOG study participants for 1973 through 1987 were assigned to the 130 regression equations. Staff at the CARB used the regression equations and every 6th day 24 hour TSP concentrations to form regression estimates of 24 hour mean concentrations of PM10 at monitoring stations throughout California for every 6th day for the years 1973 through 1987. These daily values were then cumulated to form monthly mean concentrations of indirectly estimated PM10 and monthly exceedance frequency and excess concentration indices at each station. These were then interpolated to the centroids of study participant's home and work zip codes according to the methods used for TSP, described in section 2.2 above. As for TSP, cumulations were then conducted first over months and then over time periods. A detailed assessment of precision of actual monitored PM10 is given in Table 1 of paper 15, that for indirectly estimated PM10 as compared to actual monitored PM10 in Table 2 of paper 15.

Some of the PM10 data (5,883 of 14,314 data points), which had been used to form regression equations of PM10 on TSP, was later deemed not to satisfy EPA quality criteria for control of temperature and humidity during weighing of the monitored sample. The suspect data was deleted and regression equations recomputed. Comparison of original and recomputed regression equations indicated that the deviations in the values of the regression coefficients were

well within the range of other sources of error incurred in the indirect estimation process. Hence, the suspect values were used, since including them gave better representation of paired PM10/TSP data in time and geographical location. Details of this comparison are given at the end of Appendix E.

§ 2.7 Indirect Estimation of PM2.5

This section outlines how indirect estimates of ambient concentrations of PM2.5 were formed using airport visibility data. Full details of the estimation methods are given in Appendix D, and a somewhat condensed version in the Methods section of Paper 17.

Because PM2.5 was never monitored on a consistent statewide basis, an indirect method for estimating PM2.5 was necessary. Three methods were compared for forming indirect estimates of PM2.5: 1) using site seasonal specific regressions of available monitored PM2.5 on airport visibility data applied to airport visibility data for nine California airports for the years 1966-1986; 2) using a national regression equation developed by Trijonis to estimate PM2.5 from airport visibility data; 3) forming site seasonal specific regressions of monitored PM2.5 on TSP from data where both were measured simultaneously. The average R^2 over 18 site seasonal specific regressions for the estimating PM2.5 from airport visibility was 0.577; the average R^2 for estimating PM2.5 from TSP was 0.414. The 95% confidence intervals for the intercept and slope coefficients in the site seasonal specific regression equations for estimating PM2.5 from visibility contained the Trijonis coefficients in only two areas and both of these areas required seasonal regressions, whereas Trijonis' equation was non-seasonal. Hence, method (1) was chosen. The remainder of this section describes how the estimates were formed.

PM2.5 was estimated from daily visibility data for the years 1966 - 1986 at ten California airports. Pechan and Associates obtained the data from the National Climatic Center, cleaned the data and converted visibility estimates to data extinction coefficients using a modified Koschmieder formula. This formula incorporated a contrast detection threshold and a correction factor for the relative humidity observed that day. Observations for which fog or precipitation were concurrently recorded were excluded. Days for which two good readings were not available were excluded. Visibility distances were abstracted for three different hours of each day, 10:00 a.m., 1:00 p.m., and 4:00 p.m.. The arithmatic mean distance of visibility was then computed and converted to the extension coefficient as described above.

PM2.5 was monitored by the CARB for the years 1979 through 1986. Twenty-four hour concentrations were monitored every sixth day. Though PM2.5 was not monitored on a statewide basis during these years, sufficient data existed to allow the formation of airport and seasonal specific regression equations relating PM2.5 to visibility for up to two seasons of the years for all of the 10 airports, except Stockton. There was no monitored PM2.5 data in the vicinity of Stockton. The remainder of the airports, except San Diego, had monitored PM2.5 data available for every calendar month. San Diego was missing monitored PM2.5 data for the months of July through December.

The airport areas and number of days on which paired observations of monitored PM2.5 and visibility were available for forming regression equations are shown in Table 1 of Paper 17. The number of study subjects living in each area in 1987 are also given in this table as well as the estimated ambient mean concentration of PM2.5, 1966-1986. A split-halves procedure, in which half of the paired data was used to estimate the regression coefficient and the other half to correlate estimated with actual PM2.5 values, indicated a correlation of 0.82.

Using the regression equations and the daily visibility measures, 24 hour mean concentrations of ambient PM2.5 were estimated for each airport area for all days of the years 1966-1986 with sufficient acceptable visibility data. Daily mean concentrations were converted to monthly mean concentrations. In addition to this, the percentage of days where mean concentration exceeded each of a number of different cutoff levels was computed. The cutoff levels chosen were 20, 30, and 40 $\mu g/m^3$. The percentage of days was converted to hours in excess of the cutoffs for comparability with similar exceedance frequency statistics for gaseous pollutants.

Geographic areas surrounding each airport for which airport estimates of PM2.5 could be considered as being representative of the surrounding area were identified by a team of study epidemiologists and staff from CARB with expertise in fine particulate estimation. The Ontario airport area was divided into three subareas with separate regressions being formed for each because of the large number of study subjects living in this area and the availability of a large number of paired PM2.5 and visibility data points from which to form regression equations for different subregions. Zip codes in each geographic area were given an A or B quality rating according to how well the airport estimate might represent the values at the zip code centroid. Monthly estimated mean concentrations of PM2.5 and exceedance frequency statistics were then cumulated for study participants according to zip code by month residence histories. All study subjects had reported in 1976 that they had lived the previous ten years within five miles of their present residence. Missing value algorithms were used in some cases to interpolate values where days were missing within a month and to assign values to missing months. Individuals were not included in health effects analyses unless at least 80% of their months of residence had hard data, i.e., were months where 75% of the more or more of the days had actual data and were not interpolated by missing value algorithms. This left a cohort of 1,868 individuals from the 3,914 originally selected.

In addition to estimating ambient mean concentration of PM2.5 for study participants, an adjustment was made to reflect time spent indoors. Study participants were asked in 1977 and again in 1987, how many hours per week they spent outside of buildings during the months of June through September, versus October through May. Based on studies of penetration of ambient mean concentrations of PM10 to indoor environments, an adjustment factor of 0.8 (Winer, 1989) was applied to the estimated hours spent indoors each month. Distributions of ambient mean concentration, adjusted mean ambient concentration and exceedances for each of the cutoffs 20, 30 and 40 $\mu g/m^3$ are given for study participants in Figures 1-5 of Paper 17.

For most health effects analyses, these continuous variable measures were used. However, because of the tri-modal distribution of unadjusted estimated mean concentration of PM2.5 which can be seen in Figure 1 of Paper 17, subjects were also classified into three groups according to average ambient concentration of PM2.5 1966-1986 - low, less than 20 $\mu g/m^3$; medium 20-39 $\mu g/m^3$, and high, 40 $\mu g/m^3$ or greater. A similar classification was made for the airport areas and plots of mean concentration by year were made for the low, medium, and high groupings to determine if there were time trends. These plots are shown in Figure 6 of Paper 17. No time trends were apparent except for the high area - Ontario East, which showed a decrease over time but still remained the highest area. Time plots of individual stations were also examined to determine if estimated annual mean concentrations of PM2.5 at individual airports stayed within the group classification of low, medium, or high over time. All airports stayed within their group classification except for San Jose and Ontario Central. Estimated PM2.5 for San Jose gradually increased over the 20 year time period beginning at the high end of the low grouping and ending at the low end of the medium grouping. Annual estimated mean concentrations for Ontario Central started at the low end of the high grouping and gradually decreased to the high end of the medium grouping. The time plots for individual airports are displayed in Figures 1 through 11 of Appendix F.

Table 2.1. Pollutants and Cut-offs Used For AHSMOG Study.

Ozone	
10 pphm	Old California 1 hour Standard for Total Oxidants, Now 9 pphm
12 pphm	National Primary 1-hour Standard
15 pphm	
20 pphm	First Stage Alert Level (1-hour average)
25 pphm	
NO_2	
5 pphm	National Primary Annual Average Standard is 5.3 pphm
15 pphm	
20 pphm	
25 pphm	California 1 hour Standard
SO_2	
2 pphm	
4 pphm	Present California 24-hour Standard
5 pphm	Former California 24 hour Standard
8 pphm	
14 pphm	National Primary 24 hour Standard
SO_4	
6 $\mu g/m^3$	
9 $\mu g/m^3$	
12 $\mu g/m^3$	
15 $\mu g/m^3$	
TSP	
60 $\mu g/m^3$	California Annual Average Standard
75 $\mu g/m^3$	National Primary Annual Average Standard
100 $\mu g/m^3$	California 24 hour Standard
150 $\mu g/m^3$	National Secondary Annual Average Standard
200 $\mu g/m^3$	
PM2.5	
20 $\mu g/m^3$	
30 $\mu g/m^3$	
40 $\mu g/m^3$	
PM10	
40 $\mu g/m^3$	
50 $\mu g/m^3$	California 24 hour Standard, National Primary and Secondary Standard for Annual Arithmetic Mean
60 $\mu g/m^3$	
80 $\mu g/m^3$	
100 $\mu g/m^3$	

Table 2.2. Distance Categories of Quality Ratings and Adjustment Factors for Indoor Penetration.

Pollutant and Indoor Adjustment Factor	Distance Categories of Quality Ratings		
	A	B	C
Ozone 0.5	10 mi (16 km)	20 mi (32 km)	31.25 mi (50 km)
NO_2[1]	5 mi (8 km)	10 mi (16 km)	31.25 mi (50 km)
SO_2 0.6	3 mi (4.8 km)	6 mi (9.6 km)	31.25 mi (50 km)
SO_4 0.4	20 mi (32 km)	31.25 mi (50 km)	
TSP 0.4	3 mi (4.8 km)	6 mi (9.6 km)	31.25 mi (50 km)
PM2.5 0.8	Established on Airport/Zip Code Maps		
PM10 0.7	3 mi (4.8 km)	10 mi (16 km)	31.25 mi (50 km)

(1) Regression models which incorporated indoor sources as well as adjusting ambient concentration were used.

Table 2.3 Comparisons Between Interpolated and Actual Mean Concentrations at Monitoring Stations for Pollutants used in the AHSMOG Study (1985 through 1986*).

Pollutant	Number of Stations	Actual mean	Interpolated Mean	Paired t	p	Correlation
TSP	142	63.0 $\mu g/m^3$	65.7 $\mu g/m^3$	1.85	0.07	0.83
Ozone	126	2.24 pphm	2.19 pphm	-1.41	0.20	0.87
NO_2	72	3.39 pphm	3.50 pphm	1.00	0.32	0.92
SO_2	57	0.103 pphm	0.105 pphm	0.17	0.87	0.64
SO_4	72	5.12 $\mu g/m^3$	5.41 $\mu g/m^3$	1.79	0.08	0.84
PM10**	39	45.7 $\mu g/m^3$	45.4 $\mu g/m^3$	-0.22	0.83	0.88
Indirectly estimated PM10***	39	45.7 $\mu g/m^3$	42.8 $\mu g/m^3$	-2.33	0.03	0.86

* Monthly means were first interpolated from the up to three nearest monitoring stations, then averaged over the two years period; then compared to the two year average of the actual monitored values at the station.

** The comparison is between interpolations of actual PM10 monitored at surrounding stations and actual PM10 monitored at receptor station.

*** The comparison is between interpolations of PM10 estimated from TSP concentrations at surrounding stations and actual PM10 monitored at the receptor station. This comparison checks the overall precision of both the estimation method and the interpolation method for PM10 estimated from TSP.

Chapter 3

Epidemiological and Statistical Methods

§ 3.1 Survey Methods in 1977

In March, 1977, a respiratory symptoms and residence history questionnaire was mailed out to 8,572 members of the National Cancer Institute Adventist Health Study, who satisfied the criteria listed below. The respiratory symptoms questions were developed originally by the British Medical Research Council, and modified in 1971 for use in the U.S., by the National Heart and Lung Institute (NHLI, now National Heart, Lung, and Blood Institute NHLBI). The complete questionnaire with response percentages recorded for questions is given in Appendix A. The questionnaire was used to ascertain self-reported symptoms of chronic respiratory disease. In addition, detailed smoking histories were obtained as well as histories of having lived or worked with a smoker and the duration of these exposures. Residence and work location histories since 1966 were ascertained by month and zip code. The questionnaire also ascertained lifestyle factors pertinent to relative air pollution exposures, such as occupation exposures, hours spent on crowed freeways, percent of time spent indoors/outdoors, etc.

The inclusion criteria for being mailed an AHSMOG questionnaire in March, 1977, were as follows:

- Must have resided in California and be enumerated by the 1974 Adventist Health Study census questionnaire.
- Completed a detailed Adventist Health Study lifestyle questionnaire, which was mailed out in August, 1976, and be 25 years or older at the time of the census questionnaire in 1974.
- Be a baptized member of the SDA Church at the time of enrollment in the Adventist Health Study.
- Have reported on his/her Adventist Health Study lifestyle questionnaire, he/she had lived 10 years or longer within five miles of his/her present residence.
- Resided in one of three metropolitan areas at the time of completing the Adventist Health Study lifestyle questionnaire or had been selected by a systematic random sample of 862 individuals from the rest of California. The three metropolitan areas in California which were included were: the San Diego metropolitan area, the South Coast (SCAB) Air Basin (Los Angeles and vicinity), and the San Francisco metropolitan Bay area. These areas were defined by zip code boundaries on zip code maps. Sketches of the areas are given in **Figures 3.1, 3.2, and 3.3.**

The geographic boundaries of the target population for San Francisco were defined by zip code using population density maps so as to include the surrounding metropolitan area. A similar procedure was used to define the boundaries of the San Diego Metropolitan Area. In the SCAB region the boundaries were adjusted to include a portion of the Southeast Desert Air Basin known to have significant levels of oxidants and to exclude the southern edge of the SCAB where oxidant levels and population density were much lower than the rest of the area.

A follow-up mailing was conducted in May, 1977. Non-respondents to this mailing were called on the telephone and encouraged to fill out the questionnaire. If they had not received it, they were mailed another copy. The following tracing procedures were used for those who did not respond after three telephone attempts: directory assistance, church telephone directories, calling the reference person given in the Adventist Health Study census questionnaire for the correct address or telephone number of the non-respondents, and checking with the church clerk and/or the church paster to obtain current address or telephone number. Tracing of non-respondents was completed by February 1978. In November 1978, it was discovered that 234 individuals living in the SCAB had been missed due to having post office box zip codes not listed on the zip code map. Twenty-sex individuals living near the southern boundary of the region in Corona (zip code 91720) and Perris (zip code 92370) had also been missed. A special mailing was sent to these individuals to obtain their AHSMOG questionnaires. When follow-up had been completed AHSMOG questionnaires were obtained from 7445 individuals giving a response rate of 87%. Tracing was completed and live or dead status ascertained on all but 109 individuals who could not be located. Nonresponse rates were similar inside and outside the SCAB and ranged from 14.3% to 10.4% respectively.

One-hundred and nine individuals who indicated on the questionnaire that they were currently smoking were excluded from all analyses. The health effects analyses pertaining to 1977 prevalence of respiratory disease symptoms are described in Papers 1, 2, and 3. The analyses of Paper 1 are further restricted to individuals who had resided either only inside the SCAB or only in California outside the SCAB during the previous 10 years.

Of the 7,445 who completed AHSMOG questionnaires in 1977, the Adventist Health Study followed 6,467 through 1982 for incidence ascertainment of cancer and myocardial infarction. Only individuals who were non Hispanic white were included for incidence ascertainment. This excluded 978 of the 7,445 who had completed the 1977 questionnaires. The flow chart of **Figure 3.4** diagrams the various subgroups. Of the 6,467 eligible for cancer incidence follow-up, complete cancer incidence ascertainment and follow-up was attained through 1982, on 6,340. This group defined the cancer incidence cohort on which ascertainment of myocardial infarction was obtained as well. Some of these individuals had died by 1982 but complete residence history tracking and disease surveillance was obtained on them through annual mailings of hospital history forms.

§ 3.2 Survey Methods in 1987

In April, 1987, follow-up questionnaires were mailed to 5,261 individuals (see **Figure 3.4**) who had not refused continued participation in this study since 1977, and were not known to be deceased. This questionnaire reascertained respiratory symptoms using the same questions as used in 1977 plus additional questions from the American Thoracic Society (ATS) questionnaire. Residence and work location histories were updated, as well as housing and lifestyle characteristics pertinent to relative exposures to ambient air pollutants. Mail and telephone follow-up was conducted using techniques similar to the 1977 survey. At the end of follow-up 4,725 respondents were obtained. If individuals who refused to participate are included in the denominator as well as those assumed living and willing to participate, this gives a response fraction of 87%.

Before health effects analyses were begun the following individuals were excluded from those who responded: those who reported smoking since 1977, those who were missing any respiratory symptoms questions necessary for determining presence of respiratory symptoms complexes in 1977 and 1987, individuals failing reliability criteria between the 1977 and 1987 questionnaires - primarily dealing with questions on history of respiratory disease (see section 3.7 below). After these exclusions, 3,914 individuals were available for health effects analyses. These individuals comprise what is referred to in the remainder of the report as the respiratory symptoms cohort.

§ 3.3 Cancer Incidence Ascertainment

The number of females in the cancer incidence cohort was 4,063; the number of males 2,277. Frequency distributions of covariates for the incidence cohort are given in Table 3.1 *Table 1 of Paper 7.* Table 3.2 *Table 3 of Paper 7* gives the sex specific distribution of organ and site specific cancer incidence in the cohort. The surveillance system consisted of annual mailings to every member of the cohort from 1977 through 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 for 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) (Beeson, et al., 1990).

Categories of cancer incidence outcomes which were used for health effects analyses were: all malignant neoplasms (ICDO, 140-199) in males, all malignant neoplasms in females, and respiratory cancers (ICDO, 160-165).

§ 3.4 Myocardial Incidence

Incidence of myocardial infarction was ascertained using the same surveillance as for cancer. The occurrence of incidence of myocardial infarction was documented by careful review of hospital records, including electrocardiographic readings, by a cardiologist on the study staff. For both cancer and myocardial infarction, incidence events were considered for the time period, April 1, 1977 through December 1, 1982.

§ 3.5 All Natural Cause Mortality

All natural cause mortality (ICD9 000-799) was ascertained during the period April 1, 1977 through December 31, 1986. 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).

§ 3.6 Respiratory Symptoms Complexes

Standardized respiratory symptoms questions developed originally by the British Medical Research Council, and modified in 1977, for use in the U.S. by the National Heart and Lung Institute (NHLI), now the National Heart, Lung and Blood Institute (NHLBI), were completed by study subjects in April, 1977 and again in April, 1987. Computer algorithms developed by Hodgkin (see Paper 1) were applied to the 21 respiratory symptoms questions to classify individuals as having no symptoms or possible or definite symptoms for each of chronic bronchitis, asthma, emphysema. We also classified subjects with respect to a composite respiratory disease condition which was named airway obstructive disease (AOD); (AOD was called chronic obstructive pulmonary disease (COPD) in the 1977 analyses.) A subject with possible symptoms of one or more of chronic bronchitis, asthma, and emphysema is said to have possible symptoms of AOD, and definite symptoms of AOD are defined analogously. These algorithms are given in Appendix B.

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 new cases of emphysema to warrant separate analyses, emphysema was not analyzed as a separate outcome, but it was included under AOD. Table 2 of Paper 1 lists the respiratory

symptoms which were used and gives the percentage of individuals having each symptom in 1977.

A new 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. In addition to performing health effects analyses concerning development of new cases of each respiratory symptoms complex, we also conducted analyses pertaining to persistent prevalence, i.e., having definite symptoms in 1977 and in 1987. For each respiratory symptoms complex a severity score was also developed; this score ranged from 0-10, with 10 indicating the greater severity. The scores are defined in Appendix B.

§ 3.7 Reliability Checks for Symptoms Reporting

Internal reliability of self-reporting of respiratory symptoms was conducted by cross-checking the 1977 and 1987 questionnaire responses. Individuals which failed these reliability checks because of inconsistent responses were excluded from health effects analyses. An example of failure to meet a reliability check would be reporting "Yes" to the question "Has a physician ever told you, that you have asthma in 1977," and reporting "No," to that question in 1987. Table 1, Appendix B, gives sex and age specific rates for each respiratory symptoms complex. The rates included are: prevalence in 1977; prevalence in 1987; cumulative incidence rate 1977-1987; reversal rate 1977-1987; and persistent prevalence, i.e., prevalence in both 1977 and 1987. Those individuals failing the internal reliability checks are excluded from this table.

The reliability of subjects' reports that a physician had told them they had asthma was checked by obtaining their medical charts from personal physicians. We were able to obtain complete medical information from physicians for 49 of the 84 new cases of asthma reported in 1987, among those who did not have asthma in 1977. The physicians' records confirmed prevalence of asthma between 1977 and 1987, in 30 of the 49 subjects. Health analyses pertaining to the asthma respiratory symptoms complex were rerun as a sensitivity analysis restricting cases to those who were physician confirmed.

§ 3.8 Statistical Methods for Incidence of Cancer and Myocardial Infarction and All Natural Cause Mortality

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 cutoffs were used as indices for long-term ambient concentrations of TSP and OZ. Two cutpoints for each index of ambient concentration were determined from the index's cumulative distributions for the subcohort who had resided only inside and the subcohort who had resided only outside the SCAB of California during the preceding ten years. There was not much overlap between the distributions of the generally lower ambient concentrations outside the SCAB and ambient concentrations inside the SCAB to which these subcohorts had been exposed. 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 inside SCAB concentrations that were above the lower cutpoint.

Cox proportional hazards regression models for the cancer incidence and mortality outcomes which controlled for several covariates were fitted to the data. Cox proportional hazards regression models, Cox (1972), are the model of choice for the cancer incidence and mortality outcomes where time to event in the cohort is the variable of primary interest. These models control for several covariates and were fitted by the BMDP2L stepwise procedure Dixon (1983). The covariates for each disease model are listed in Table 4.8 *Table 7 of Paper 7.*

Cumulative ambient concentrations of TSP and ozone were represented by annual average concentrations and annual average exceedance frequencies above cutoffs for two time periods (1/66-3/77 and 1/73-3/77). The later time period was allowed as an alternative for the longer time period in the models because 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 cutoff. Time-dependent Cox regression 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 ozone were fitted separately. Models were first fit for TSP using exceedance frequencies for the cutoff of 200 micrograms per cubic meter (TSP200) and ozone using exceedance frequencies for the cutoff of 10 pphm (OZ10). For other pollutants, unless otherwise specified, models were first fit for ambient mean concentration of a pollutant. For each pollutant the variables selected for these cutoffs were then used for the other cutoffs 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 (1987). Using age as the time variable provides a tighter control and adjustment for

age. This is especially important for disease outcomes which are strongly age related. 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 experienced high exposures is given in Paper 2.

The pollutant exposure variable or variables and the secondary candidate variables competed for entry by the stepwise selection procedure. For an initial run, a P-value for the F to remove of 0.15 and a P-value for the F to enter of 0.10 were used to terminate the stepwise procedure. After examination of the increase in R^2 at each step in the initial run, the stepwise procedure was stopped where the increase in R^2 began to plateau. All final models chosen had a P-value for the F to enter of 0.05 or less.

Interactions between the pollutant variable and the other covariates were assessed by entering first order cross product turns in the model and then removing them and noting the change in the log likelihood. No statistically significant interactions were observed.

§ 3.9 Statistical Methods for Analyses of 1987 Respiratory Symptoms Outcomes

§ 3.9a General Description of Models and Covariates Used

For each of the three diseases - AOD, chronic bronchitis, and asthma, - separate multiple logistic regression models were used for studying associations between long-term cumulative ambient concentrations of air pollution and new cases of definite symptoms among individuals who did not have definite symptoms in 1977. For each disease, individuals having possible symptoms of that disease 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. For each disease, the 1977 symptoms severity score for that disease was used as a covariate in the analysis. 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 3.3 *Table 1 of Paper 8*, 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, ozone, and SO_2 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. For analyses pertaining to gaseous pollutants, the form of occupational air pollutants

utilized as a candidate variable was fume exposure at work. For analyses pertaining to particulate pollutants, the form of occupational pollutants used as a candidate variable was dust exposure at work.

The above analyses excluded individuals who had definite symptoms in 1977. In order to allow these individuals to be included, we used the change in the symptoms 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. The same set of candidate covariates as the multiple logistic regressions were used for the models with the exception that the variable "whether or not the individual had possible symptoms of the disease in 1977" was replaced by the 1977 symptoms 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.

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. These three time periods were used rather than just one since exposure patterns changed over time for some individuals. For ambient concentration variables "lifetime" was replaced with cumulations since 1973, which were 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.

Pollutants for which exceptions to the above procedure were made were suspended sulfates, (SO_4), and fine particulates <2.5 microns in diameter, (PM2.5). SO_4 data was only available for the time period 1977 through 1987, so this was the only time period used in models. PM2.5 estimates were based on airport visibility measures which were available for 10 airports in California 1966-1986; thus the time periods used for PM2.5 were 1966 through March, 1977, and April 1977 through 1987, as well as the entire time period 1966 through April 1987.

The different time periods for pollutant 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 time period that contributed best to the model

rather than to arbitrarily force in one or the other of the forms. Thus for some models the "through 1977" form of a pollutant was selected, while the "through 1987" or 1977-1987 time period was selected for others.

Stepwise regression analyses were run separately for each pollutant and for each exceedance frequency of a pollutant (i.e. they were not allowed to compete for entry into the same model). This was done to avoid problems of multicolinearity which might arise because of high correlations between different exceedance frequencies of the same pollutant and also of high correlations between some pollutants. The cutoff levels of 200 $\mu g/m^3$ for TSP, 10 pphm for ozone (OZ10) and 4 pphm for SO_2 ($SO_2(4)$) were used for initial model determination, since they were the most significantly related to prevalence of AOD in previous analyses (see Paper 4). For most other pollutants, unless otherwise noted, the initial model utilized ambient mean concentration. Once a final model for each pollutant was determined, the model was repeated, retaining the same set of covariates (but allowing their regression coefficients to change) for the other cutoff levels of the pollutant as well as for the mean concentration. Finally, multi-pollutant models on which pollutants 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 pollutant exposure variable (for example - TSP200, OZ10, or $SO_2(4)$) if it was significant. These terms were added to the existing models to determine if they significantly improved the fit of the model. None of the interaction terms was significant on any of the models.

Sensitivity analyses were conducted to assess the impact of interpolation error on results. Final models were re-run restricting interpolation quality to A or B quality and requiring individuals to have at least 80% A or B quality data. The A, B, and C, quality ratings were defined in Table 2.2. The sensitivity analyses were conducted for the final models for the cancer incidence, incidence of MI, and all natural cause mortality analyses as well as the respiratory symptoms outcomes. In every case concurrence with results reported in subsequent chapters was obtained.

§ 3.9b Calculating Relative Risk From Multiple Logistic Regression

The appropriate multivariate statistical model to use for development of definite symptoms of, or prevalence of, a respiratory symptoms complex is the multiple logistic regression model, where the probability of an event, y, is modeled by,

(3.1)

$$y = \frac{1}{1 + e^{-(\alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots)}}$$

In our present application of this model, y would be the probability of an individual reporting definite symptoms of AOD, x_1 would be the air pollution exposure variable under study, the other x's would be covariates such as occupational exposure, years lived with a smoker, years worked with a smoker, sex, age, etc.

The odds of an event, as modelled by the multiple logistic regression model is given by

(3.2)

$$\frac{y}{1-y} = e^{\alpha+\beta_1 x_1+\beta_2 x_2+\cdots}.$$

The odds ratio or relative odds for a specific variable, say x_1, is given by e^{β}_1. The estimated odds ratio for a *k*-unit increase in x_1 with the other variables held constant has been shown by Kahn (1983), to be equal to $e^{k\beta}_1$. For air pollution standards setting, it is more meaningful to talk about relative risk rather than relative odds. The relative odds for a *k*-unit increase can be converted to relative risk using the formula given in Paper 4:

(3.3)

$$RR \text{ for } k \text{ unit increase} = \frac{e^{k\beta_1}}{1 - P_0 + P_0 e^{k\beta_1}}$$

$$\text{where } P_0 = \text{Probability of event given no exposure to } x_1$$

Note that P_0 can be estimated from the sample data, using the number of cases of the event occurring at zero level exposure to x_1 divided by the size of the reference group, the population at zero level exposure to x_1. In air pollution research, where there is rarely an actual "zero level" exposure, we would use a low level exposure to define a reference group.

The values of P_0 used for each air pollutant variable and covariate for which relative risk calculations were made is given in Table 3.4, for development of definite symptoms of AOD, chronic bronchitis, and asthma. For example, for AOD, P_0 is estimated for each variable as the number of individuals with little or no exposure who developed definite symptoms of AOD, between 1977 - 1987 divided by the number with little or no exposure who did not have definite symptoms in 1987. For the air pollutant variables P_0 was calculated for those in the lowest quintile of the distribution of ambient mean concentration for each pollutant. For the variables - years smoked in the past, years lived with smoker, years worked with a smoker, the P_0 was calculated for those who had no exposure for each variable. For example, for years smoked in the past the rate would be calculated in those who had never smoked. For dummy variables

such as possible symptoms in 1977, childhood AOD, and gender, the rate would be calculated for the value of "0" of the dummy variable, which for possible symptoms was those with no symptoms in 1977; for childhood AOD, those with no childhood AOD and for gender, females. For frequency of childhood colds which was a 5 point Likert type scale, the value of P_0 was calculated for those indicating the lowest category. For age, P_0 was calculated in those who are in the lowest quintile of the age distribution. For education P_0 was calculated for those who had an education at level of 8th grade or less.

We will now show how the relative risks (RR) and 95% confidence intervals (C.I.) for relative risks in tables such as Table 4.1 are calculated. We first explain the calculation for an air pollution exposure variable. An increment of exposure for calculating RR was chosen which spans the range of values of the variable but leaves at least 10% of the cohort with higher values to avoid extrapolation. For hours in excess of 200 $\mu g/m^3$ of TSP (TSP 200) the value k of 1,000 hours (42 days) per year was chosen. From **Figure 18** of Appendix F we can see that a value of 1,000 hours or 42 days per year almost spans the range of the distribution of exceedance frequency above 200 $\mu g/m^3$ of TSP (TSP 200), leaving 11% of the cohort with greater exposures. We now substitute k = 1,000, P_0 = .075 from Table 3.4, and β_1 = .0003339 from Table 4.1, in equation 3.3 to give the RR of developing AOD for a 1,000 hour increase in TSP200.

(3.4)

$$RR = \frac{e^{(1{,}000)\ (0.0003339)}}{1 - 0.075 + 0.075\, e^{(1{,}000)\ (0.000339)}}$$
$$= 1.36$$

This gives a RR of developing AOD of 1.36 for a 1,000 hour per year increase in TSP200. The 95% C.I. for this RR according to a Taylor series first order approximation to variance is obtained by substituting the lower and upper bounds of the 95% C.I. for β_1 into equation 3.3. This was accomplished by replacing β_1 with $\beta_1 \pm 1.96\ SE\beta_1$ in equation 3.4. The 95% C.I. for β_1 for TSP200 is 1.11 to 1.66.

An example of the RR calculation for a dummy variable type covariate, "possible symptoms in 1977," is now given. A dummy variable has values of 0 or 1. Thus the variable of possible symptoms of AOD can be denoted by x_2.

$$x_2 = \begin{cases} 1 \text{ if possible symptoms of AOD in 1977} \\ 0 \text{ otherwise in 1977} \end{cases}$$

Note that the value of $x_2 = 0$ for "otherwise" is equivalent to no symptoms in 1977 since those with definite symptoms in 1977 are not at risk for developing symptoms and are excluded from these analyses pertaining to development of symptoms.

To calculate the RR of developing definite AOD for those with possible symptoms in 1977, compared to those with no symptoms, we substitute the estimated regression coefficient for possible symptoms in 1977 from Table 4.1, which is 1.30778, into equation 3.3 along with the value of $k = 1$ and the value of P_0 of 0.086 from Table 3.4. This gives a RR of

(3.5)

$$\textit{RR for possible symptoms in } 1977 = \frac{e^{(1)\,(1.30778)}}{1 - .086 + .086\, e^{(1)\,(1.30778)}} = 3.00$$

The 95% C.I. for this RR is calculated in the same manner as for TSP200 by substituting the lower and upper bound of the 95% C.I. for β_1 in equation 3.5.

Using this procedure, RRs were calculated for additional increments of TSP200 of 250 hours and 500 hours per year respectively, see Table 4.4. To obtain the RR estimates for a different cutoff, e.g., 150 $\mu g/m^3$, the multiple logistic regression model is again fitted to the data using as the exposure variable this time, exceedance frequencies for 150 $\mu g/m^3$ of TSP. A new estimated regression coefficient is obtained, new values of k are chosen, again so as not to exceed the range experienced by the cohort, and point estimates of RR calculated. This procedure is repeated for each cutoff level to generate the RR estimates of Table 4.4. Thus, to generate the risk estimates of Table 4.4, six multiple logistic regression models had to be fitted to the data for each of AOD, chronic bronchitis, and asthma, giving a total of 18 multiple logistic regression models which were fitted to the data.

A graphical presentation of the data in Table 4.4 can be made, see **Figure 3.6** *Figure 1 of Paper 8*. Each of the lines in **Figure 3.6** show how the RR increases for fixed numbers of hours (days) per year of ambient concentrations above different cutoff levels, e.g., 1,000 hours per year in excess of 200 $\mu g/m^3$ results in a RR of 1.37 while 1,000 hours per year in excess of 150 $\mu g/m^3$ results in an estimated RR of 1.15 for development of symptoms of AOD. **Figure 3.6** can be used as a guide for standards setting by examining the curves to see where the RR begins to increase rapidly as a function of increasing cutoff levels. From **Figure 3.6** we see that the curves are fairly flat for 60 and 75 $\mu g/m^3$ and begin to rise sharply after 100 $\mu g/m^3$, and also that the lower cutoffs of 60 and 75 $\mu g/m^3$ lack statistical significance. Thus a prudent standard would be the national standard of 75 $\mu g/m^3$. Graphs such as those in **Figure 3.6** which plot relative risk for fixed increments of exceedance frequency against cutoff levels will be referred to in this report as RR plots.

If one wished to keep the RR to the general public of developing a certain disease below a specified level, an alternative way of plotting RR, a RR contour plot, see **Figure 3.7** *Figure 2 of Paper 8* may be useful. This plot shows hours (days) per year plotted against different cutoffs for different curves which hold the RR constant. By keeping the cutoff and hours per year in excess of that cutoff below a specified curve, the RR of that curve will not be exceeded. Thus, if one were to say that the maximum RR allowable for the population was 1.2, a 20% increase, then levels of ambient TSP should be kept below 2,500 hours per year in excess of 100 $\mu g/m^3$, for example, reading values off the 1.2 RR contour plot in **Figure 3.7**. This of course assumes that the general population experiences the same RR of disease/ambient concentration relationship as the study cohort.

To facilitate generating the (x, y) points needed for **Figure 3.7** it is helpful to rearrange equation 3.3 as

(3.6)

$$k = \frac{1}{\beta_1} \ln \left(\frac{1 - P_0}{R^{-1} - P_0} \right)$$

where R denotes relative risk, RR

In order to use equation (3.6) to generate a RR contour plot, one must first choose a disease outcome and pollutant. This choice determines P_0. For AOD and TSP, $P_0 = .075$ from Table 3.4. Next one must choose the RR which one wishes to form a contour plot for, say $R = 1.3$. Substituting $R = 1.3$ and $P_0 = .075$ into equation 3.6 gives

(3.7)

$$k = \frac{1}{\beta_1} \ln (1.3329)$$

Now one can select the different cutoff levels from Table 2.1 for which exceedance frequencies were generated for the chosen pollutant. The TSP the cutoff levels were 60, 75, 100, 150, and 200 $\mu g/m^3$. These cutoff levels are the points on the x axis of the RR contour plot for which values of k on the y axis are computed. For each cutoff level an estimated value of β_1 is determined from the multiple logistic regressions for that pollutant cutoff and disease outcome. For the cutoff of 200 $\mu g/m^3$ of TSP and AOD, $\beta_1 = .0003339$ from Table 4.3. Substituting this

into equation (3.7) gives k = 860.5 as the point on the y axis in **Figure 3.7** corresponding to a cutoff (x value) of 200. This process is repeated for each of the 5 cutoffs to give 5 corresponding points on the y axis for the desired RR of 1.3. Note that a different multiple logistic regression and different data needs to be determined for each new cutoff.

The effort required to generate new exceedance frequency and excess concentrations statistics for additional cutoffs is extensive. It requires many hours of mainframe computer time and personnel at both CARB and LLU. Thus cutoff levels for any new pollutant must be chosen very carefully and far in advance of health effects analyses.

Additional details and examples for interpreting RR and RR contour plots are given in Paper 4.

TABLE 3.1 *Table 1 of 7* **Frequency Distributions of Past and Passive Smoking Variables and Covariates in the AHSMOG Incidence Cohort.**

VARIABLE	FEMALES N = 4,063		MALES N = 2,277	
History of Smoking	No.	(%)	No.	(%)
Never	3504	(86)	1450	(64)
Past Only	559	(14)	827	(36)
Pack Years of Cigarette Smoking				
None	3475	(86)	1484	(65)
< 10 pack years	335	(08)	339	(15)
≥ 10 pack years	196	(05)	390	(17)
Unknown	57	(01)	64	(03)
Total Years of Smoking				
Never	3519	(87)	1507	(66)
1-9 years	292	(07)	312	(14)
≥ 10 years	246	(06)	429	(19)
Unknown	6	(01)	30	(01)
Age (4-1-77)				
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)
Education				
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)
Occupational Air Pollution				
No	4026	(99)	1964	(86)
Yes	37	(01)	313	(14)
Years lived with a smoker				
Never	2119	(52)	1508	(66)
1-9 years	403	(10)	236	(10)
≥ 10 years	1541	(38)	533	(23)
Unknown	-0-	(0)	-0-	(0)
Years worked with a smoker				
Never	2512	(62)	1183	(52)
1-9 years	815	(20)	392	(17)
≥ 10 years	736	(18)	702	(31)
Unknown	-0-	(0)	-0-	(0)
Residence in South Coast Air Basin*		(Both Sexes)		
Outside		2043	(32)	
Inside		3914	(62)	
Mixed		383	(06)	

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

TABLE 3.2 ***Table 3 of Paper 7*** **Sex Specific Distribution of Organ-Site Specific Cancer in the AHSMOG Incidence Population.**

Site	Females No.	(%)	Males No.	(%)
Colon	22	(12)	17	(15)
Rectum	12	(6)	3	(3)
Pancreas	8	(4)	0	(0)
Lung	5	(3)	12	(11)
Leukemia	6	(3)	6	(5)
Skin	9	(5)	16	(14)
Breast	65	(34)	0	(0)
Cervix	5	(13)	0	(0)
Uterine	37	(20)	0	(0)
Ovary	10	(5)	0	(0)
Thyroid	4	(2)	0	(0)
Bladder	0	(0)	7	(6)
Lymphoma	6	(3)	9	(8)
Prostate	0	(0)	42	(38)
Total	189	(100)	112	(100)

Table 3.3 ***Table 1 of Paper 8*** **Descriptive Statistics for Candidate Independent Variables for Stepwise Regressions For AOD Symptoms, Chronic Bronchitis Symptoms, and Asthma Symptoms. (n = 3914)**

Mean	Max. Value	%=0	Primary Variables (Forced Into Regressions)
-	-	64.0	Gender (0 = females, 1 = males)
55.9	95	-	Age - April 1, 1977
13.9	19	-	Years Education - 1977
			Secondary Variables
			Ambient Air Pollutants
394.6	2277	2.0	TSP (average annual hours in excess of 200 $\mu g/m^3$, 1973-1987).
337.0	966	0.0	Ozone (average annual hours in excess of 10 pphm, 1973-1987).
42.9	202	0.7	SO_2 (average annual hours in excess of 4 pphm, 1973-1987).
			Past and Passive Smoking
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)
			Occupational Air Pollutants
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)
			Previous Respiratory Symptoms
2.5	5		Frequency of childhood colds (1=much less, 2=less, 3=same, 4=more,
-	-	91.8	5=much more than other children of the same age.)
			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)

The mean values for age, education, TSP, ozone, and SO_2 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.

Table 3.4 Estimated Probabilities P_O for Relative Risk Calculations - Probabilities of Developing Definite Symptoms of AOD, Chronic Bronchitis, or Asthma for Subjects with Little or No Exposure to the Pollutant or Zero Value of the Covariate.

Variable	AOD	Chronic Bronchitis	Asthma
TSP	0.075	0.066	0.020
PM10	0.082	0.071	0.021
PM2.5	0.064	0.032	0.021
SO_4	0.069	0.062	0.017
Ozone	0.081	0.067	0.019
NO_2	0.156	0.121	0.056
SO_2	0.092	0.077	0.032
Years Smoked in Past	0.080	0.067	0.021
Years Worked with Smoker	0.071	0.061	0.016
Possible Symptoms in 1977	0.086	0.073	0.022
Childhood AOD	0.079	0.069	0.018
Frequency of Childhood Colds	0.065	0.052	0.017
Gender (0 = female)	0.079	0.065	0.023
Age	0.080	0.054	0.035
Education	0.115	0.082	0.029

Map 1

San Francisco Area

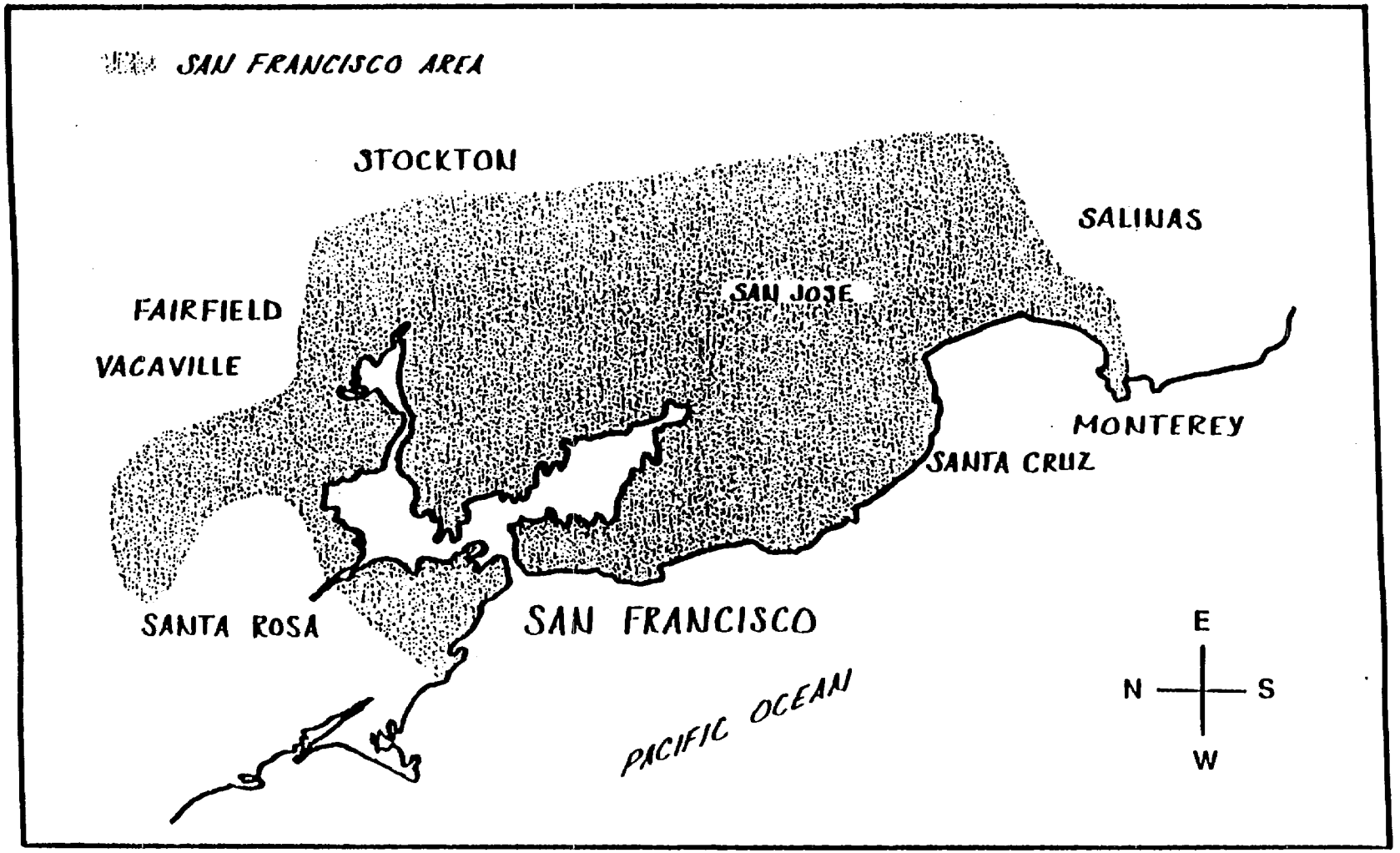


Figure 3.1. Geographic Boundaries for San Francisco

Map 2
San Diego Area

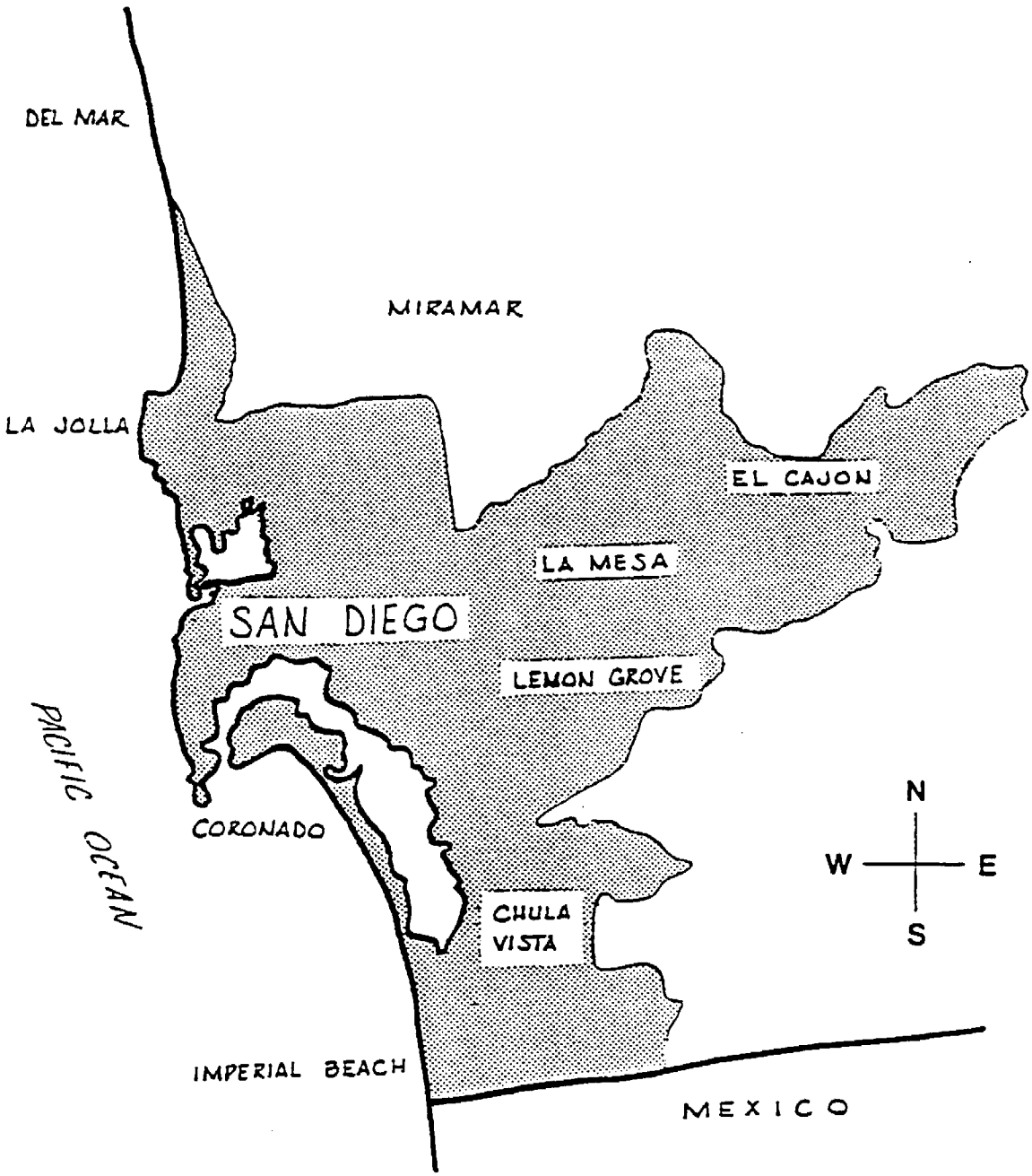


Figure 3.2. Geographic Boundaries for San Diego.

Map 3
South Coast Air Basin (SCAB)

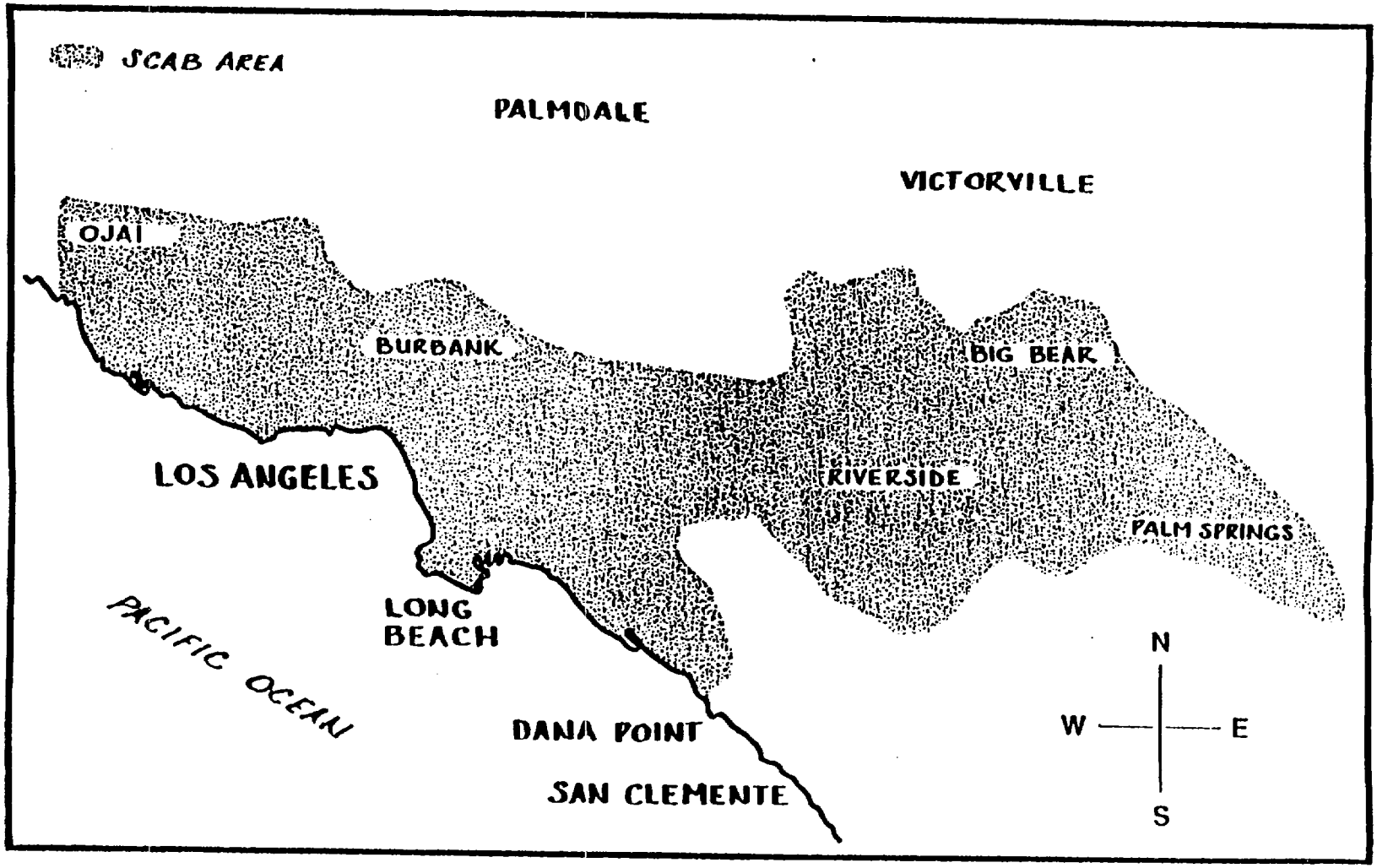


Figure 3.3.Geographic boundaries for South Coast Air Basin (SCAB).

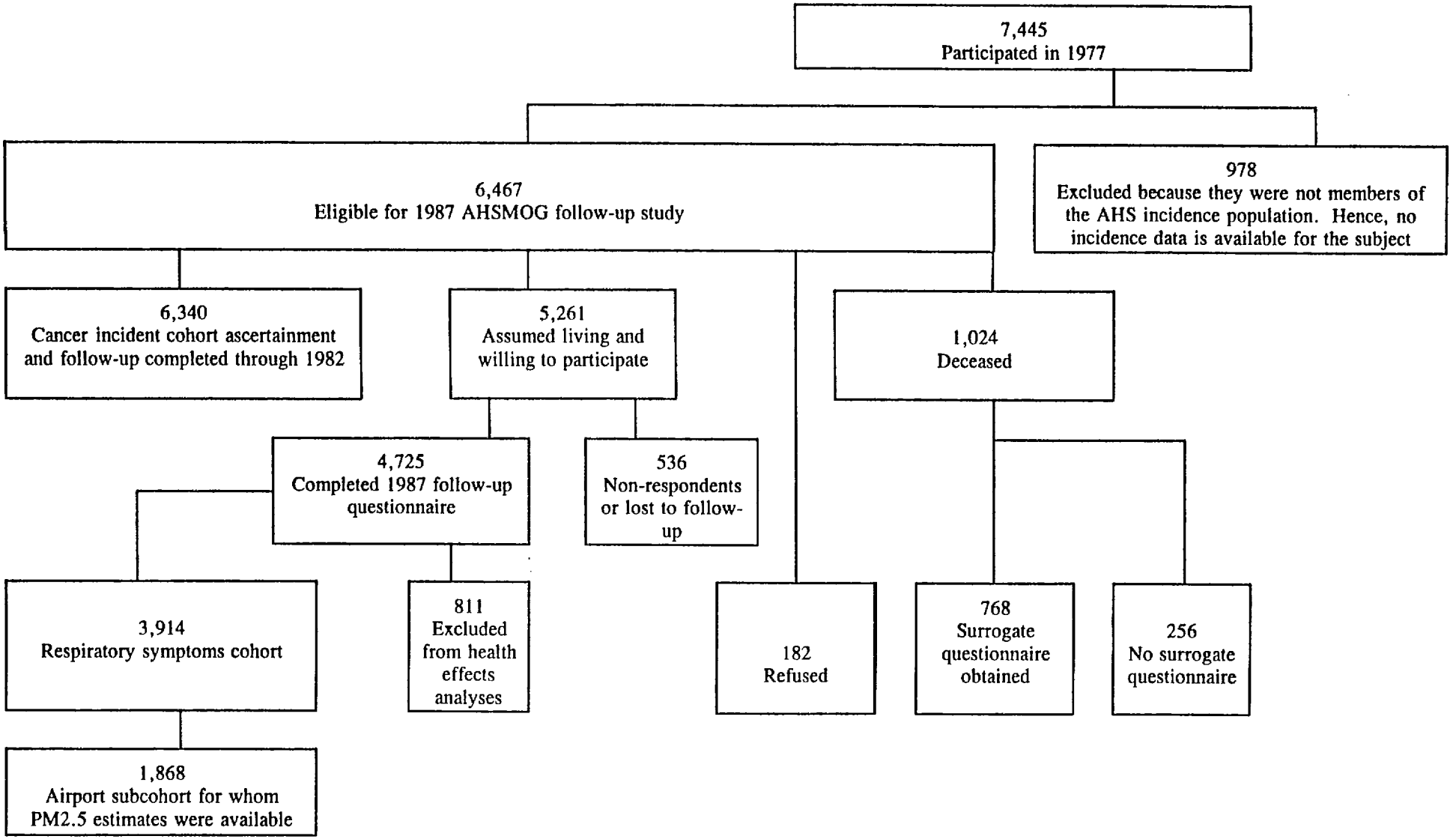
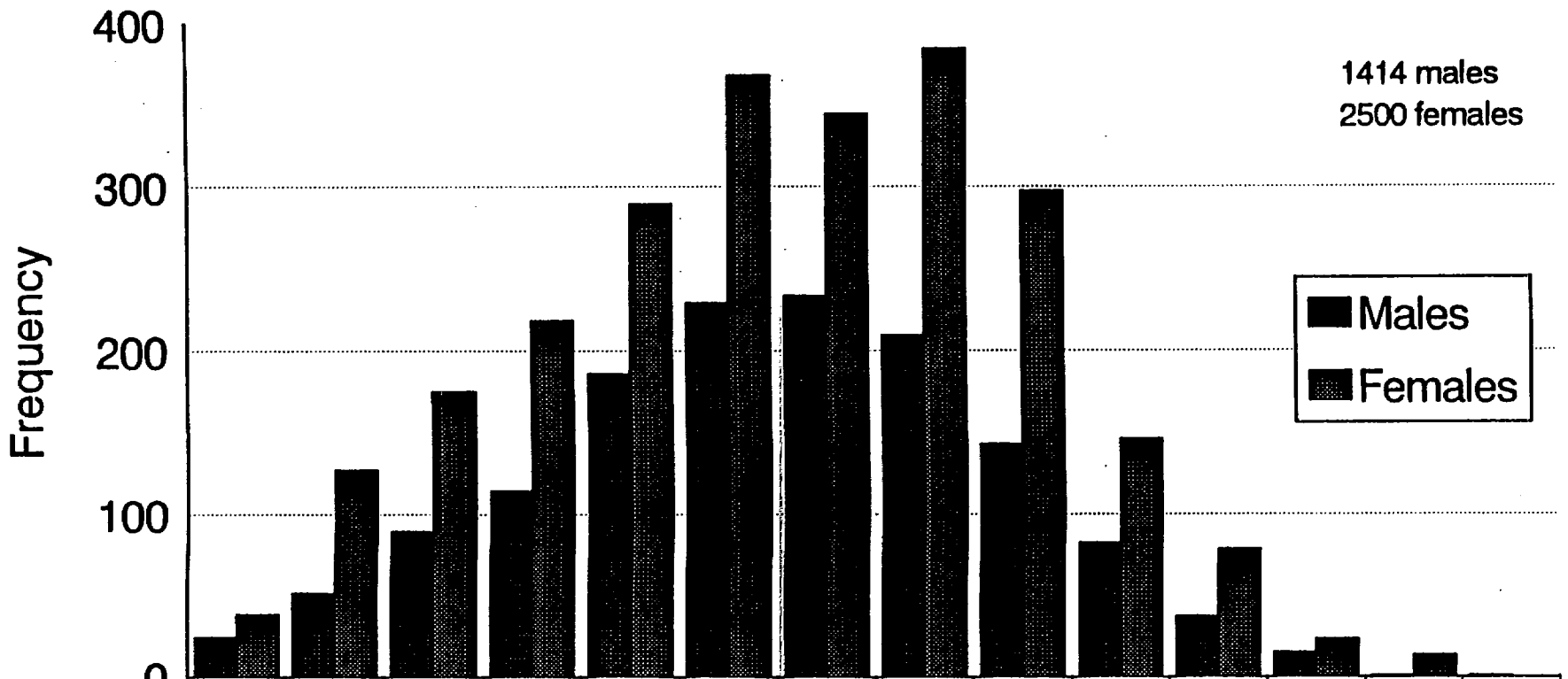


FIGURE 3.4 AHSMOG Flow Chart



	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	81-85	86-90	91-95
Males	24	51	89	114	186	229	233	209	143	82	37	15	1	1
Females	38	127	175	218	289	368	344	384	297	146	78	23	13	0

Figure 3.5 . Age Distribution by Gender as of 1977.

For the Respiratory Symptoms Cohort
(n = 3914)

RELATIVE RISK FOR ALL CUTOFFS

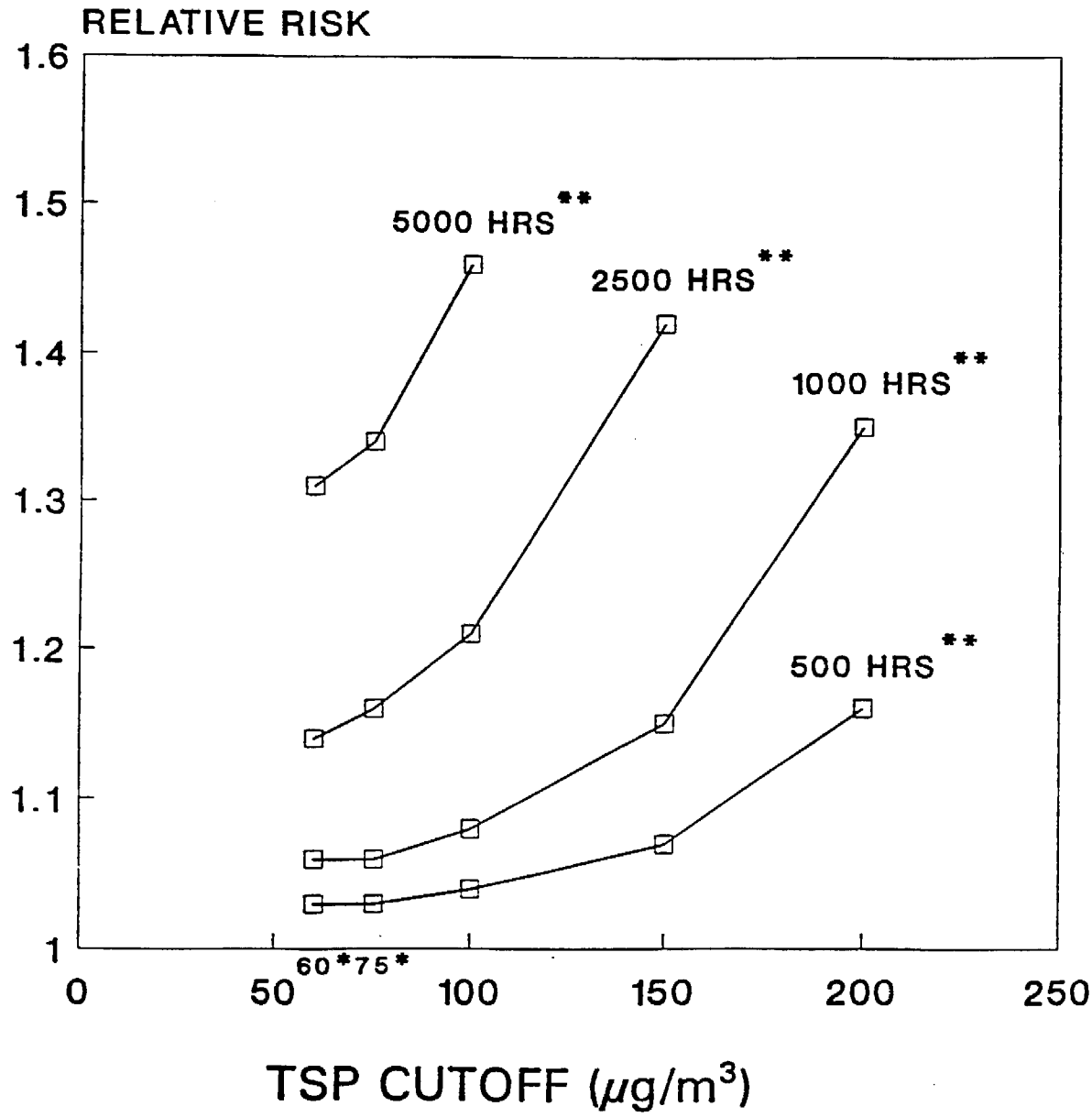


Fig. 3.6 **Relative Risk of New Cases of Definite Symptoms of Airway Obstructive Disease in 1987 for Differing Annual Average Hours in Excess of 60, 75, 100, 150, and 200 $\mu g/m^3$ of Total Suspended Particulates.**

* Risks for lowest cutoffs of 60 and 75 $\mu g/m^3$ are not statistically significant.

** Average annual hours, 1973-1977.

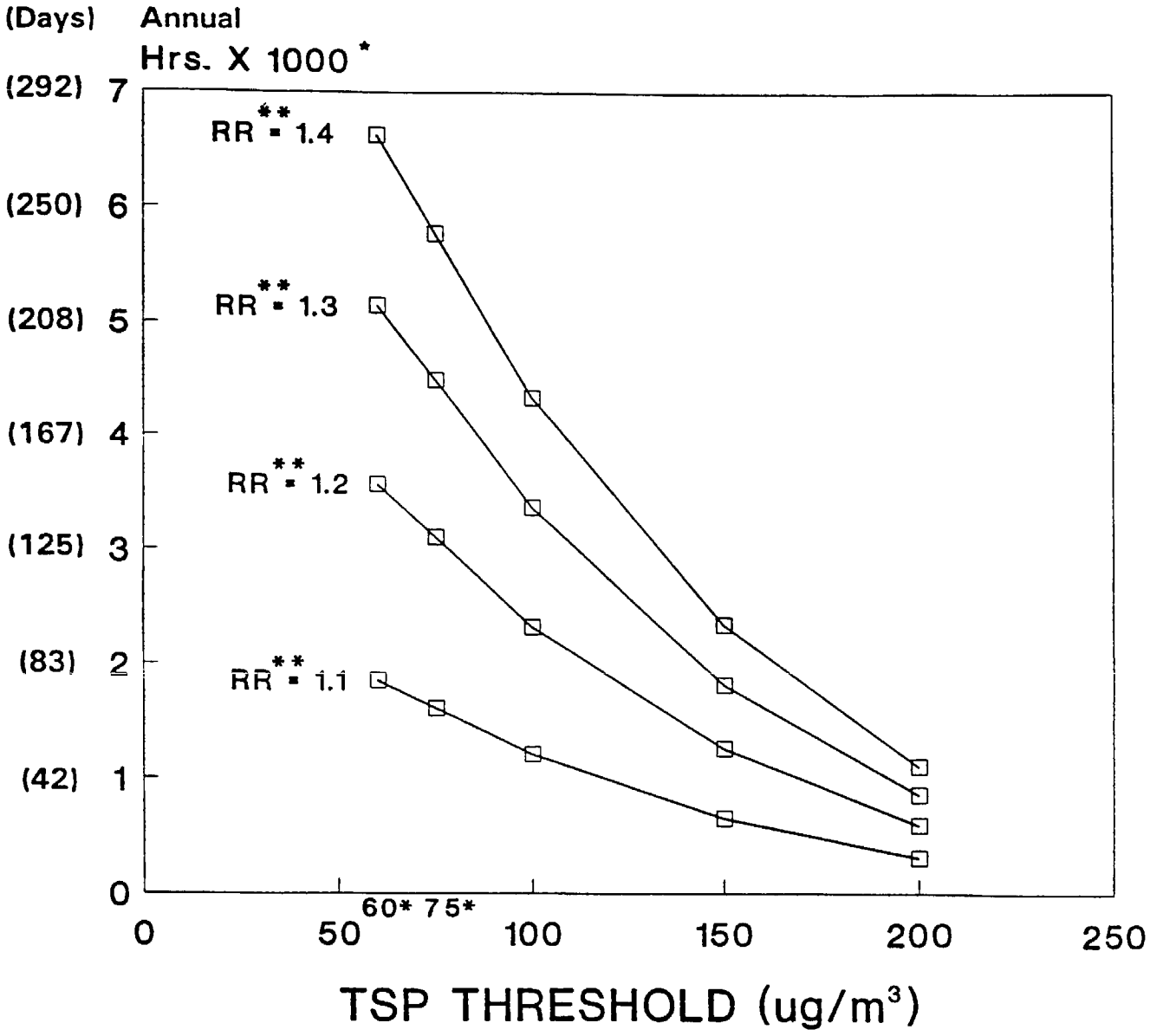


Fig. 3.7 Relative Risk Contour Plots for New Cases of Definite Symptoms of AOD Associated with TSP.

* Average annual hours, 1973-1977.

** Relative Risks for Cutoffs of 60 and 75 $\mu g/m^3$ are not statistically significant.

Chapter 4

Health Effects Associated with Long-Term Ambient Concentrations of Total Suspended Particulates

§ 4.1 Introduction

The frequency distribution for average mean concentration and average annual exceedance frequency statistics of TSP for the entire cohort are given in Figures 1 and 3 of Paper 5. Selected distributions for the respiratory symptoms cohort are given in Figures 12-18 of Appendix F.

§ 4.2 Development of AOD

Development of new cases of definite symptoms of AOD was statistically significantly related to long-term ambient concentrations of total suspended particulates. The multiple logistic regression model relating new cases of definite symptoms of AOD to average annual hours 1973-1977 in excess of 200 $\mu g/m^3$ TSP is given in Table 4.1 *Table 2 of Paper 8.* A 1000 hours/year (42 days/year) increase in ambient concentrations of TSP in excess of 200 $\mu g/m^3$ was statistically significantly associated with a 36% increase in relative risk of developing definite symptoms of AOD ($p < 0.01$). Other cutoffs which shows statistically significant association with development of definite symptoms of AOD were 100, 150 and 150 $\mu g/m^3$ as well as annual mean concentration. Relative risks corresponding to different increments of ambient concentrations above these cutoffs are shown in Table 4.4 *Table 5 of Paper 8.* Relative risk (RR) plots and RR contour plots are given in Figures 1 and 2 respectively, of Paper 8. There were no statistically significant associations between exceedance frequencies in excess of 60 and 75 $\mu g/m^3$ and development of definite symptoms of AOD. Three time periods for averaging TSP concentrations - 1/1/73 through 3/31/77; 4/1/77 through 3/31/87, and 1/1/73 through 3/31/87 were allowed to compete for entry in the stepwise regression procedures used to form statistical models. For TSP, the time which was most related to the development of symptoms was 1/1/73 through 3/31/77.

§ 4.3 Development of Chronic Bronchitis

New cases of definite chronic bronchitis symptoms were statistically significantly related to long-term ambient concentrations of TSP. Table 4.2 *Table 3 of Paper 8* gives the multiple logistic regression model relating average annual exceedances of TSP in excess of 200 $\mu g/m^3$ with development of chronic bronchitis. An increment of 1000 hours/year (42 days/year) was statistically significantly associated with a 33% increased relative risk for development of chronic bronchitis symptoms ($p < 0.05$). Other cutoffs for which exceedance frequencies were related to development of chronic bronchitis were 100, 150 and 200 $\mu g/m^3$ as well as mean

concentration. The relative risks associated with various increments above these cutoffs are shown in Table 4.4 *Table 5 of Paper 8*. There were no statistically significant associations for exceedance frequencies above 60 or 75 $\mu g/m^3$ of TSP with development of chronic bronchitis. The time period of ambient concentrations of TSP showing the most significant relationship with chronic bronchitis was 1/1/73 through 3/31/77.

§ 4.4 Development of Asthma

Development of definite symptoms of asthma was statistically significantly associated with long-term ambient concentrations of TSP. Table 4.3 *Table 4 of Paper 8* shows the multiple logistic regression model for development of new cases of definite symptoms of asthma. An increment of 1000 hours/year (42 days/year) was statistically significantly associated ($p < 0.05$) with an increased relative risk of 74% for development of new cases of asthma. Other cutoffs for TSP showing statistically significant associations with development of asthma were 150 and 200 $\mu g/m^3$. Neither average annual mean concentration nor exceedance frequencies above 60, 75 or 100 $\mu g/m^3$ of TSP were associated were significantly associated with development of asthma. Table 4.4 *Table 5 of Paper 8* gives relative risks for various increments above the different cutoff levels.

§ 4.5 Change in Respiratory Symptoms Severity Scores

Multiple linear regression models related change in symptoms severity score 1977-1987 for AOD, chronic bronchitis and asthma to long-term ambient concentrations of TSP, see Table 4.5. The following regression coefficients for mean concentration and exceedance frequencies of TSP ambient concentrations were statistically significant at the .05 level, with increasing severity of symptoms: AOD - mean concentration and all cutoffs, chronic bronchitis - cutoffs of 150 and 200 $\mu g/m^3$, asthma - mean concentration and cutoffs 100, 105, and 200 $\mu g/m^3$. The magnitudes of the regression coefficients increased, and their tail probabilities decreased with increasing cutoff levels, indicating that a consistent dose response relationship existed. The time periods of TSP which were most significantly related to change in respiratory symptoms severity score was 1973-1987 for AOD and asthma and 1973 through 1977 for chronic bronchitis.

§ 4.6 Sensitivity Analyses

Individuals reported time spent indoors by season in 1977 and 1987. Using these reported estimates of time spent indoors an adjustment factor of 0.4 was applied to monthly ambient mean concentration of TSP to obtain an overall adjusted ambient mean concentration. This adjustment factor was obtained from work by Winer, et al. (1989). Application of the adjustment factor results in decreasing the range of concentration. Mean concentration analyses were rerun after obtaining the indoor adjustments. In general, the coefficients, adjusted for time spent indoors, were larger than the unadjusted coefficients. For every respiratory symptoms

outcome the level of statistical significance remained very close to what it was prior to adjustment.

As a check on the accuracy of interpolation from fixed site monitors to zip code centroids, interpolations were restricted to those which were within A or B quality range, considered representative by EPA (1977). The regression models for TSP 200 and TSP mean concentration were rerun with this restriction. 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 because of the reduced sample size and did not achieve the 0.05 level of statistical significance.

§ 4.7 All Malignant Neoplasms

There was a statistically significant association between incidence of all malignant neoplasms (1977-1982) in females with long-term ambient concentrations of TSP. Exceedance frequencies above 100, 150 and 200 $\mu g/m^3$ were statistically significantly associated with elevated risks. Neither mean concentration nor exceedance frequencies above 60 or 75 $\mu g/m^3$ were statistically significantly associated with increased risk though the regression coefficients were positive. The Cox Proportional Hazards Regression Model which was used to study these associations is given in Table 4.6 *Table 5 of Paper 7.* A 37% increased risk of incidence of all malignant neoplasms was associated with an increase of 1000 hours/year (42 days/year) in ambient concentrations of TSP exceeding 200 $\mu g/m^3$ for 1973 through March 1977 ($p < 0.02$). The relative risks for various increments of exceedance frequencies above other cutoffs as well as mean concentration are given in Table 4.7 *Table 8 of Paper 7.* No statistically significant associations were observed between long-term ambient concentrations of TSP and incidence of all malignant neoplasms in males. See Table 4.7 *Table 8 of Paper 7.*

§ 4.8 Respiratory Cancers

There were 17 incident cases of smoking related respiratory cancers. The Cox Proportional Hazards Regression Model was used to study association of long-term ambient concentrations of TSP, 1973-1977, with incidence of respiratory cancers adjusting for gender, total years smoked in the past and education. The regression model used age as time on study. The model is shown in Table 4.8 *Table 7 of Paper 7.* A 1,000 hour/year increase in TSP in excess of 200 $\mu g/m^3$ gave an increase in relative risk of 72% according to the model but this association was not statistically significant due to the small number of incident cases. There were no statistically significant associations between long-term ambient concentrations in excess of other cutoff levels or for mean concentration of TSP and incidence of smoking related respiratory cancers. The relative risks for these other cutoffs as well as mean concentration are given in Table 4.7 *Table 8 of Paper 7.*

§ 4.9 Cancer Mortality

Cox Proportional Hazards Regression Models were also fit to mortality data for 1977 through 1986. Covariates included total years of smoking and education (as a surrogate measure of social class). Past or present experience in a occupation of high levels of airborne contaminants was also included for the males but not for females due to minimal exposure of females in such occupations. Increasing average annual hours of exposure to TSP above the various cutoffs 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 cutoffs of TSP were of borderline statistical significance ($p=0.04$ - 0.06).

§ 4.10 Sensitivity Analyses for Cancer Outcomes: Time Spent Indoors and Restriction to High Quality Exposure Data

Average time spent indoors by season was ascertained from study participants in 1977 and again in 1987. Using these estimates of time spent indoors an adjustment factor of 0.4 was applied to mean ambient concentrations of TSP to represent an indoor infiltration factor of ambient concentrations. This adjustment factor was obtained from Winer, et al. (1989). The results of applying the adjustment factor to mean concentration were to scale down the estimates of ambient concentration. This resulted in increases in the regression coefficients. Statistical significance for each of the outcomes reported above also increased.

Another sensitivity analysis restricted interpolations to be within the A or B quality ranges which are considered representative by the EPA (1977). The final regression models for TSP 200 and TSP mean concentration were rerun with this restriction. The number of individuals available for analysis was reduced by approximately one-half. The regression coefficients were essentially unchanged for cancer outcomes after these restriction criteria were applied.

§ 4.11 Incidence of Myocardial Infarction (MI)

Incidence of MI 1977 through 1982 was evaluated in relation to ambient TSP levels. The relationships between MI and exceedance frequencies above 60 $\mu g/m^3$ was almost statistically significant and a slight increase in risk was associated with those exceedance frequencies (in both the stratified analyses and the Cox Proportional Hazards Regression Analysis). However, none of the exceedance frequencies above other cutoff levels was associated with increased risk nor was there increased risk associated with mean concentration of TSP. Table 4.9 *Table 2 of Paper 5* gives the point estimate of relative risk and confidence interval for exceedance frequencies above 200 $\mu g/m^3$ as associated with incidence of MI. This table also gives the other covariates used in the Cox Proportional Hazards Regression Model.

§ 4.12 All Natural Cause Mortality

No statistically significant associations were observed between all natural cause mortality from 1977 through 1986 and mean concentration or exceedance frequencies for the various cutoffs of TSP. Table 4.9 *Table 2 of Paper 5* gives the point estimate of relative risk and 95% confidence interval for all natural cause mortality related to exceedance frequencies above TSP above 200 $\mu g/m^3$ of TSP. This table also gives the other covariates which were included in the Cox Proportional Hazards Regression Model.

Summary

Long-term ambient concentrations of TSP were found to be statistically significantly associated with elevated relative risks for development of definite symptoms of AOD and chronic bronchitis as well as asthma. Elevated incidence of all malignant neoplasms in females but not males was statistically significantly associated with long-term ambient concentrations of TSP. A trend relationship was also observed for respiratory cancers but this was not statistically significant due to the small number of only 17 incident cases . Increased risks for cancer mortality were associated with long-term ambient concentrations of TSP for males but not for females. No statistically significant associations between long-term ambient concentrations of TSP and all natural cause mortality were observed. There was a slight positive association between incidence of MI and the exceedance frequency index for 60 $\mu g/m^3$ of TSP. However, this association was not statistically significant and exceedance frequencies above higher cutoffs and mean concentration were not associated with incidence of MI.

Table 4.1 ***Table 2 of Paper 8***
Multiple Logistic Regression for New Cases of Definite Symptoms of AOD in 1987 with Hours Average Annual Concentration In Excess of 200 $\mu g/m^3$ of TSP as the Air Pollution Variable.

(n = 3,220 cases = 272)

Variable	Regression Coefficient	Increment[1]	Relative Risk [5]	95% CI for Relative Risk
TSP (Hrs. in Excess of 200 $\mu g/m^3$ [2]	0.0003339**	1000 hr/yr.	1.36	1.11, 1.66
Years Smoked	0.022531*	10 yr.	1.23	1.05, 1.43
Years Lived with Smoker [3]	0.013211*	10 yr.	1.13	1.03, 1.24
Years Worked with Smoker [4]	0.013362*	10 yr.	1.13	1.01, 1.27
Possible Symptoms in 1977	1.30778***	(0=No, 1=Yes)	3.00	2.44, 3.64
Childhood AOD	0.61056**	(0=No, 1=Yes)	1.73	1.20, 2.44
Childhood Colds	0.24882**	1	1.26	1.09, 1.45
Gender	0.192378	(0=F, 1=M)	1.19	0.91, 1.55
Age	-0.0022017	10 yr.	0.98	0.88, 1.08
Education	0.015347	4 yr.	1.06	0.88, 1.26
Constant	-2.9313			

[1] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
[2] Average annual hours in excess of 200 $\mu g/m^3$ 1973-1977.
[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 4.2 ***Table 3 of Paper 8***
Multiple Logistic Regression for New Cases of Definite Chronic Bronchitis Symptoms in 1987 With Hours Average Annual Concentration In Excess of 200 $\mu g/m^3$ of TSP as the Air Pollution Variable.

(n = 3,310, cases = 234)

Variable	Regression Coefficient	Increment[1]	Relative Risk[5]	95% CI for Relative Risk
TSP (Hrs. in Excess of 200 $\mu g/m^3$ [2]	0.00030683*	1000 hr/yr.	1.33	1.07, 1.65
Years Smoked	0.028107**	10 yr.	1.30	1.11, 1.51
Years Lived with Smoker [3]	0.015471**	10 yr.	1.15	1.05, 1.27
Possible Symptoms in 1977	1.22786***	(0=No, 1=Yes)	2.90	2.30, 3.62
Childhood Colds	0.32401***	(1)	1.37	1.17, 1.66
Gender	0.34454*	(0=F, 1=M)	1.37	1.04, 1.80
Age	0.0030717	10 yr.	1.03	0.92, 1.15
Education	0.014346	4 yr.	1.05	0.87, 1.27
Constant	-3.7835			

[1] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
[2] Average annual hours in excess of 200 $\mu g/m^3$ 1973-1977.
[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 4.3 ***Table 4 of Paper 8***
Multiple Logistic Regression for New Cases of Definite Symptoms of Asthma With Hours Average Annual Concentration In Excess of 200 $\mu g/m^3$ Of TSP as the Air Pollution Variable.

(n = 3,615, incident cases = 80)

Variable	Regression Coefficient	Increment[1]	Relative Risk[5]	95% CI for Relative Risk
TSP (Hrs. in Excess of 200 $\mu g/m^3$ [3]	0.0005687*	1000 hr/yr.	1.74	1.11, 2.72
Years Worked with Smoker [4]	0.040998***	10 yr.	1.50	1.23, 1.82
Possible Symptoms in 1977	4.0822***	(0=No, 1=Yes)	25.97	18.37, 32.90
Gender	-0.602*	(0=F, 1=M)	0.55	0.32, 0.95
Age	-0.016371	10 yr.	0.85	0.70, 1.04
Education	0.030878	4 yr.	1.13	0.77, 1.64
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 $\mu g/m^3$ 1977-1977.
[4] Years worked with smoker through 1987.

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

Table 4.4 *(Table 5 of Paper 8)*
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 Cutoff Levels of Total Suspended Particulates.

Cutoff Level	Increment[1] Size(Hours Per Year)	Percent Population Exposure	Relative Risk Estimate		
			AOD	Chronic Bronchitis	Asthma
60 $\mu g/m^3$	250	100	1.01	1.01	1.01
	500	100	1.03	1.03	1.03
	1000	99.5	1.06	1.06	1.05
	2500	95	1.14	1.15	1.14
	5000	70	1.31	1.31	1.29
75 $\mu g/m^3$	250	100	1.01	1.01	1.02
	500	99	1.03	1.03	1.03
	1000	98	1.06	1.06	1.07
	2500	80	1.16	1.14	1.17
	5000	55	1.34	1.31	1.37
100 $\mu g/m^3$	250	98	1.02*	1.02*	1.03
	500	92	1.04*	1.04*	1.05
	1000	80	1.08*	1.08*	1.11
	2500	60	1.21*	1.20*	1.29
	5000	18	1.46*	1.44*	1.67
150 $\mu g/m^3$	250	73	1.04**	1.04*	1.05*
	500	64	1.07**	1.07*	1.11*
	1000	42	1.15**	1.15*	1.23*
	2500	18	1.42**	1.41*	1.66*
200 $\mu g/m^3$	250	56	1.08***	1.08*	1.15*
	500	29	1.16***	1.16*	1.32*
	1000	11	1.35***	1.35*	1.74*
Mean Concentration	60	87	1.39*	1.36*	1.56
	75	77	1.51*	1.46*	1.74
	100	59	1.72*	1.66*	2.08
	120	24	1.91*	1.83*	2.41
	135	10	2.07*	1.96*	2.68

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

[1] Increment for computations of relative risk. Hours per year 1/1/773 through 3/31/77. Units for mean concentration are $\mu g/m^3$

Table 4.5 Linear Regression Models for Change in Symptoms Scores.

	Total Suspended Particulates						Ozone	
	AOD (N = 3,661)		Chronic Bronchitis (N = 3,680)		Asthma (N = 3,697)		Asthma (N=3634)	
Variable	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	0.44	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]	0.002	1	0.094
Years Dust Exposure at Work	7[4]	0.07	5[4]	0.06	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]	0.046		
OZ10							6	0.042[5]
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^2		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] For pollutant variables, average number of hours per year, 1973-1987. For other variables, number of years, 1973-1987.
[5] For pollutant variables, average number of hours per year, 1977-1987. For other variables, number of years, 1977-1987.
[6] Did not enter.

Table 4.6 ***(Table 5 of Paper 7)***
Cox Proportional Hazards Regression for all Malignant Neoplasms Among Females, 1977-82, with Hours Average Annual Concentration in Excess of 200 $\mu g/m^3$ of Total Suspended Particulates as the Air Pollution Exposure Variable

(n = 4,063, Cases = 175)

Variable	Regression Coefficient	Increment[2]	Relative Risk[3]	95% CI for Relative Risk
TSP (Hrs. in Excess of 200 $\mu g/m^3$)[1]	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 $\mu g/m^3$ 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 4.7 *Table 8 of Paper 7*
Estimates of Cancer Incidence (1977-82) Relative Risks from Cox Proportional Hazards Regressions for Incremental Increases of TSP (1/73 -3/77): Average Annual Exceedance Frequencies Above Various Cutoffs and Mean Concentration

Cutoff Level	% Person-months in Excess of Increment+	Increment(I) Size	All Malignant Neoplasms MALES (n = 108)	All Malignant Neoplasms FEMALES (n = 175)	Smoking Related Respiratory Cancers (n = 17)
60 $\mu g/m^3$	99.7	1000 Hrs/yr	1.04	1.05	1.21
	88.1	3500	1.13	1.18	1.96
	77.5	5000	1.19	1.27	2.62
75 $\mu g/m^3$	98.6	1000 Hrs/yr	1.04	1.07	1.19
	78.8	3500	1.13	1.27	1.82
	67.5	5000	1.19	1.41	2.36
100 $\mu g/m^3$	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 $\mu g/m^3$	67.4ǂ	500 Hrs/yr	1.00	1.09x	1.15
	54.7	1000	1.00	1.18x	1.33
	23.0	2500	0.99	1.52x	2.04
200 $\mu g/m^3$	48.8	250 Hrs/yr	0.99	1.08°	1.14
	31.5	500	0.98	1.17°	1.31
	26.9	750	0.97	1.27°	1.50
	21.3	1000	0.96	1.37°	1.72
Mean Concentration	98.3	50 $\mu g/m^3$	1.03	1.26	1.73
	60.7	100 $\mu g/m^3$	1.06	1.60	2.98

(I) Increment for computations of relative risk.
* p=0.04
x p=0.01
° p<0.02
\+ Each individual contributes a different number of months to a cohort study depending on censoring date so increment size for ambient concentrations is related to the distribution of person-months.
ǂ This % corrrect; the % published in Table 8 of Paper 7 was a typographical error.

Table 4.8 ***Table 7 of Paper 7***
Cox Proportional Hazards Regression for Respiratory Cancer, 1977-82, With Hours Average Annual Concentration in Excess of 200 $\mu g/m^3$ of Total Suspended Particulates as the Air Pollution Exposure Variable.

(N = 6301, Cases = 17)

Variable	Regression Coefficient	Increment[2]	Relative Risk[3]	95% CI for Relative Risk
TSP (Hrs. in Excess of 200 $\mu g/m^3$)[1]	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 $\mu g/m^3$ 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 4.9 *Table 2 of Paper 5*
Relative Risks for Cancer, Myocardial Infarction and All Natural Cause Mortality for Exceedance Frequencies Above 200 $\mu g/m^3$ of TSP and Above 10 pphm Ozone.

Outcome	N	1000 Hours Above TSP200	500 Hours Above Oz 10
All Malig. Neoplasms[a] 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)
Myocardial Infarction[b]	62	0.93 (0.57-1.51)	1.06 (0.69-1.61)
All Natural[c] Cause Mortality	845	0.99 (0.87-1.13)	1.00 (0.89-1.12)
Definite[(d)] AOD Symptoms	272	1.36 (1.11-1.65)[g]	1.04 (0.86-1.25)[h]
Definite[(e)] Chronic Bronchitis Symptoms	234	1.33 (1.07-1.51)[g]	1.02 (0.83-1.25)[h]
Definite Asthma[f] Symptoms	80	1.74 (1.11-1.27)[g]	1.35 (0.93-1.96)[h]

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

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

[c] Variables included in the model for mortality were (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 were (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 chronic bronchitis symptoms were (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 symptoms were (besides age) education, sex, possible symptoms in 1977 and years worked with a smoker.

[g] There was an error on the upper bound of these confidence intervals in Table 2 of Paper 5 which has been corrected in this table.

[h] There were errors on these confidence intervals or relative risks in Table 2 of Paper 5 which have been corrected in this table.

Chapter 5

Health Effects Associated with Long-Term Ambient Concentrations of Ozone

§ 5.1 Introduction

Frequency distributions for average mean concentration and average annual exceedance frequency statistics for the entire cohort are given in Figures 2 and 4 of Paper 5. The distribution of average annual hours in excess of 10 pphm ozone is given in Figure 19 of Appendix F. This chapter summarizes results given in Papers 5, 7, 8 and 13.

§ 5.2 Development of Respiratory Symptoms

Non-gender specific analyses, using gender as a covariate showed no statistically significant relationships with ozone for development of AOD, Chronic Bronchitis, or Asthma. However, a highly statistically significant association was observed between ambient mean concentration of ozone, 1973-1987, and development of asthma in males, but this association was not significant in females. The relative risk for an increase in 1 pphm of ozone was 3.12 ($p < 0.0001$), the multiple logistic regression model for males is given in Table 5.1 *Table 3 of Paper 13.* Exceedance frequencies for 10 pphm of ozone showed a statistically significant elevated risk ($p < 0.05$) for men but not for women. Neither exceedance frequencies nor excess concentrations were statistically significant for other cutoffs of ozone - 12, 15, 20, and 25 pphm.

§ 5.3 Change in Respiratory Symptoms Severity Scores

Non gender specific multiple linear regression models using gender as a covariate were formed for ozone and change in severity score for each respiratory symptoms complex. There was a statistically significant relationship only for asthma, see Table 4.5. Change in asthma severity score was significantly associated with mean concentration of ozone (1977-1987) and with the 1977-1987 average annual exceedance frequency for cutoffs of 10 pphm and 12 pphm. The nonstandardized regression coefficients were larger for the exceedance frequency of 12 pphm than for 10 pphm which implies that, on the average, fewer hours of ambient concentrations above the higher cutoff produced the same effect. Change in severity scores for the other respiratory symptoms complexes were not significantly associated with exceedance frequencies or excess concentrations for any of the cutoffs of ozone or for mean concentration.

§ 5.4 Sensitivity Analyses for Respiratory Outcomes

An indoor adjustment factor of 0.5 (Winer, 1989) was applied to ambient mean concentrations of ozone, according to estimated time spent indoors by study participants. Final models for development of symptoms and change in respiratory symptoms severity score as well as development of new cases of respiratory symptoms complexes were rerun. The statistical significance of adjusted mean concentration of ozone was very close to what it was for unadjusted mean concentration. Another sensitivity analysis was conducted for ozone and asthma, again restricting interpolations to those with A or B quality data. Because of 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 analysis. Regression coefficients agreed closely with those which were obtained when no restriction of A or B quality on interpolation ranges was imposed.

§ 5.5 Cancer Incidence

No statistically significant relationships were observed between incidence of all malignant neoplasms and long-term ambient concentrations of ozone. For respiratory cancer, however, a relative risk of 2.25 of borderline statistical significance (95% confidence interval 0.96, 5.31) was observed between ambient concentrations of 500 hours per year in excess of 10 pphm, 1973-1977. The Cox proportional hazards regression model used to establish this relationship is given in Table 5.2 *Table 9 of Paper 7.* Statistical significance was not achieved for any of the other cutoffs or for mean concentration.

§ 5.6 Cancer Mortality

There were no statistically significantly increased risks of deaths due to malignant neoplasms for ozone in either males or females.

§ 5.7 Adjustment for Time Spent Indoors and Restriction to A/B Quality Data

Sensitivity analyses were conducted applying an adjustment factor of 0.5 to mean concentration of ambient ozone according to estimated time spent indoors by study participants. For mean concentration of ozone associated with respiratory cancer, the coefficient was essentially doubled. This corresponded to a decreased range in adjusted mean concentration. The result of the adjustment procedure was to improve statistical significance of each outcome. Interpolations were restricted to those within A or B quality ranges. This reduced the number of individuals available for analysis by 6%. The regression coefficients were essentially unchanged after this restriction criteria was implied.

§ 5.8 Incidence of Myocardial Infarction

Ambient levels of ozone were not associated with altered risk of myocardial infarction for any cutoff level of ozone or for mean concentration. For 500 hours in excess of 10 pphm, the multivariate adjusted relative risk for myocardial infarction was 1.06 (95% confidence interval, 0.69 - 1.61). Table 4.9 *Table 2 of Paper 5* gives the covariates that were included in this multivariate Cox proportional hazards regression.

§ 5.9 All Natural Cause Mortality

No statistically significant relationships between all natural cause mortality (1977-1986) and ambient levels of ozone were observed. There were no statistically significant relationships for any of the cutoffs nor for mean concentration. The multivariate adjusted relative risk for all natural cause mortality as associated with 500 hours per year above 10 pphm ozone was 1.00 (95% CI, 0.89 - 1.12). The covariates included in this model are listed in Table 4.9 *Table 2 of Paper 5*.

TABLE 5.1 ***Table 3 of Paper 13***
Multiple Logistic Regression for Cumulative Crude Incidence* of Asthma between 1977 and 1987
Definite Asthma by Reported Symptoms or Reported Physician Diagnosis Developed Between 1977 and 1987 (AST87) (n = 3577, incident cases = 78)

Variable†	Coefficient	Increment‡	Relative Risk§	95% CI for Relative Risk
YWS87	0.038120‖	10 y	1.45	1.21-1.80
OX87	0.275530	1 pphm¶	1.31	0.96-1.78
AODB16	1.504500‖	No or yes	4.24	4.03-4.45
Education	0.048769	4 y	1.21	0.85-1.71
Age	-0.018012	1 y	0.98	0.96-1.00
Gender	-0.289890	M or F	0.75	0.46-1.23
Constant	-4.0270			
AST87: Sex Specific Analysis, Men Only (n = 1305, Incident cases = 27)				
YWS87	0.0412850#	10 y	1.50	1.12-2.01
OX87	1.1819000‖	1 pphm	3.12	1.61- 5.85
AODB16	2.0631000‖	No or yes	7.01	3.07-14.60
Education	0.0987410	4 y	1.46	0.85-2.49
Age	0.0032417	1 y	1.0	0.97-1.04
Constant	-8.5669			
AST87: Sex Specific Analysis, Women Only (n = 2272, Incident cases = 51)				
YWS87	0.0412350#	10 y	1.50	1.17-1.92
OX87	-0.0656010	1 pphm	0.94	0.65-1.34
AODB16	1.2562000‖	No or yes	3.36	1.72-6.38
Education	0.0146030	4 y	1.06	0.65-1.71
Age	-0.0280350*	1 y	0.97	0.95-1.00
Constant	-2.0905			

* Crude incidence because information on those who died is missing.

† YWS87, years ever worked with a smoker through 1987; OX87, average ambient ozone concentration 1973 - 1987; AODB16, history of obstructive airways disease before age 16.

‡ Increment for computations of relative risks.

§ Relative risk of increase in exposure of one increment, holding the other variables in the model constant.

¶ pphm; part per hundred million.

‖ $P < .001$.

\# $P < .01$.

** $P < .05$.

Table 5.2 ***Table 9 of Paper 7***
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)

Variable	Regression Coefficient	Increment[2]	Relative Risk[3]	95% C.I. for Relative Risk
Oxidants (Hrs. in Excess of 10 pphm)[1]	0.0016256+	1500 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.

* $p < 0.05$
\+ $p = 0.055$

Chapter 6

Health Effects of Long Term Concentrations of SO_2

§ 6.1 Introduction

Ambient mean concentrations and exceedance frequency statistics in excess of 2, 4, 5, 6, 8, and 14 pphm were calculated for SO_2 for the time periods 1966 through March, 1977; 1973 through March, 1977; 1973 through March, 1987; and April 1977 through March, 1987. Figures 1-6 of Paper 11, show the frequency distributions of ambient mean concentrations of SO_2 as well as for exceedance frequencies above various cutoffs for the cancer incidence cohort. This chapter summarizes results reported in Papers 8 and 11.

§ 6.2 Respiratory Health Effects

The same steps in model formation as outlined for ozone in Chapter 5, were used. No statistically significant relationships between SO_2 and any of the respiratory symptoms outcomes were found. Because of this, multipollutant analyses involving SO_2 were not conducted. Average ambient concentrations of SO_2 experienced by our population were relatively low. For example, the highest decile of our population had an annual ambient mean concentration of only 1.01 pphm and experienced average annual ambient concentrations above 2 pphm and 4 pphm of only 373 hours and 112 hours, respectively. This may be the reason for the lack of statistical significance between health effects and SO_2 in our population. An adjustment factor for indoor infiltration of 0.6 provided by Winer (1989), was applied to ambient mean concentration of SO_2 according to time spent indoors as estimated from information obtained on subjects' questionnaires in 1977 and 1987. The range for SO_2 mean concentration in the cohort decreased from 0 - 1.90 pphm before adjustment to 0 - 0.84 pphm after adjustment, with the average mean concentration for the cohort decreasing from 0.63 pphm to 0.28 pphm.

§ 6.3 Sensitivity Analyses for Respiratory Outcomes

Respiratory health effects analyses were rerun after applying the indoor adjustment factor; again, no statistically significant effects were observed. Restriction to A or B quality interpolations also did not change the lack of statistically significant associations between SO_2 and health effects. However, the magnitude and statistical significance of the regression coefficient for development of new cases of AOD was increased, almost reaching statistical significance for the cutoff of 4 pphm. (Published results pertaining to SO_2 are contained in Paper 8.)

§ 6.4 Other Chronic Disease Outcomes

Possible associations between long term ambient concentrations of SO_2 and incidence of all malignant neoplasms in males, incidence of all malignant neoplasms in females, smoking related respiratory cancers, incidence of myocardial infarction, respiratory disease mortality, and all natural cause mortality were assessed using statistical methods similar to those for ozone. No statistically significant associations with SO_2 and any of these outcomes were observed. Further details of these analyses are given in Paper 11.

§ 6.5 Sensitivity Analyses for Other Chronic Disease Outcomes

Sensitivity analyses re-ran models for mean concentration after applying an indoor adjustment factor of 0.6, Winer (1989), and then again restricting interpolations to be within A or B quality range. No statistically significant associations were seen in these sensitivity analyses.

Chapter 7

Health Effects of Long Term Ambient Concentrations of Suspended Sulfates, SO_4.

§ 7.1 Introduction

Ambient mean concentrations, exceedance frequencies and excess concentrations for cutoffs 6, 9, 12, and 15 $\mu g/m^3$ of suspended sulfates (SO_4), were estimated for study participants for the time period 1977 though 1987. The distributions of these statistics for the cancer incidence cohort are given in Figures 6 through 11 of Paper 11. SO_4 data were not available on a statewide basis prior to 1977. The distributions of ambient mean concentration of SO_4 (1977-1987) as well as adjusted ambient mean concentration of SO_4 for this time period for the cohort who completed respiratory symptoms questionnaires in 1977 and 1987, are given in Figures 1 and 2 of Paper 9. This chapter summarizes results reported in Papers 9 and 11.

§ 7.2 Development of Respiratory Symptoms

Multiple logistic regression models were developed for new cases of definite symptoms of AOD, chronic bronchitis, and asthma as well as "doctor told asthma." For asthma the covariate "possible symptoms in 1977" was not included in the initial model as explained further below. Ten year ambient mean concentrations of SO_4 showed a statistically significant ($p < .05$) association with development of definite symptoms of asthma but failed to show a significant association with any of the other health outcomes. Table 7.1 *Table 2 of Paper 9* gives the multiple logistics regression model for development of definite symptoms of asthma. Note that the model is similar to that for TSP, (compare Table 4.3) except that the covariate "possible symptoms in 1977" has not been included. This results in the covariate "AOD before age 16," entering the model and the covariate "years worked with a smoker 1977-1987" replacing "years worked with a smoker-lifetime through 1987." The multiple logistic regression models were rerun using as the exposure variable each of the ten year cumulative exceedance frequency statistics for the various cutoffs of SO_4. These also failed to show statistically significant associations with these health outcomes. Analyses were repeated for mean concentration using persistent prevalence as the health outcome variable. Again, no statistically significant associations were found.

§ 7.3 Change in Respiratory Symptoms Severity Score

The above analyses excluded individuals who had definite symptoms in 1977. In order to allow these individuals to be included, we used the change in symptoms 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. The same set of candidate covariates as were used in the multiple logistic regressions were used for the models with the exception that the variable "whether or not the individual had possible symptoms of the disease in 1977" was replaced by the 1977 symptoms score.

SO_4 was not associated with change in severity of chronic bronchitis or asthma but was statistically significantly associated with change in severity of AOD for average annual exceedance frequency above 6 $\mu g/m^3$, see Table 7.2. Neither mean concentration of SO_4 nor exceedance frequencies above the other cutoffs showed a statistically significant association with change in severity of AOD symptoms. Though exceedance frequencies for the higher cutoffs were not statistically significant, the regression coefficients showed a dose response relationship. A sub-analysis on the 320 individuals who reported definite AOD symptoms in 1977 failed to show any associations with SO_4 and changing symptoms severity between 1977 and 1987. Another sub-analysis on the 154 individuals who reported in 1977 that a doctor had told them they had asthma failed to show an association between change in asthma severity score and SO_4.

§ 7.4 Sensitivity Analyses Including/Excluding the 1977 Possible Symptoms Covariate or Symptoms Score Covariate.

The covariates "possible symptoms in 1977" for the multiple logistic regression models and "1977 symptoms score" for the multiple linear regression models were strongly associated with health outcomes. Since study participants had lived in their same neighborhoods for 10 or more years, it is possible that SO_4 exposure prior to 1977, though not measured, may have contributed to development of symptoms in 1977. Hence, to control for 1977 symptoms may result in diluting effects. To check on this possibility, the models were run both including and excluding this covariate. Results agreed closely with the models presented in the tables except for the multiple logistic regression model for new cases of definite symptoms of asthma. For "doctor told asthma" symptoms were not involved in the definition and hence were not used as a covariate.

For comparability of asthma results with those for other pollutants, the model for new cases of definite symptoms of asthma excluding "possible symptoms in 1977" as a covariate is presented in Table 7.1 *Table 2 of Paper 9.* When "possible symptoms in 1977" was included as a covariate, the regression coefficient for SO_4 remained essentially unchanged though the statistical significance changed slightly to $p = .054$. The variable "Childhood AOD" was no longer statistically significant and failed to enter the model. This is understandable as childhood AOD would be expected to be associated with "possible symptoms in 1977" since it was associated with development of definite symptoms in 1987. The regression coefficient for "Years worked with a smoker," remained highly statistically significant but decreased in magnitude giving a resultant relative risk estimate of 1.50 for a ten year increment. The time period for this variable changed from "1977 to 1987" to "through 1987." The regression coefficients for age, gender, and education remained nonsignificant.

§ 7.5 Are Observed Results Due to Surrogate Relationships with Other Pollutants?

Statistically significant associations were observed for change in symptoms severity score for AOD and SO_4 exceedances above the cutoff of 6 $\mu g/m^3$, [SO_4 (6)]. Also, significant associations for new cases of asthma with SO_4 mean concentration were observed when the 1977 possible symptoms covariate was excluded. A question which arises concerning these findings is, "Are they possibly due to a surrogate relationship with another pollutant?" To investigate this possibility, we conducted multipollutant analyses for these health outcomes for the pollutants TSP, ozone, SO_4, and SO_2.

TSP but neither SO_2 nor ozone were significantly related to change in AOD symptoms severity, see Paper 8. Of the TSP exceedance frequency statistics, SO_4 (6) was most highly correlated with exceedance frequencies of TSP above 60 $\mu g/m^3$ (TSP60) $r = 0.78$. Thus, a multipollutant analysis was conducted for change in AOD symptoms severity score in which the final linear regression model for SO_4 (6) was used and TSP60 and SO_4 (6) were allowed to compete for entry after the other covariates had been forced into the model. TSP60 came into the model before SO_4. Once TSP was in the model, SO_4 failed to make a statistically significant additional contribution. Although TSP60 came in before SO_4, other exceedance frequency levels of TSP were more significantly related to change in AOD severity score, most notably TSP200. These analyses suggest that SO_4 may be serving as a surrogate for TSP for change in symptoms severity of AOD.

A statistically significant association was seen between development of new cases of asthma and ambient mean concentrations (1977-1987) of SO_4. TSP and ozone were also statistically significantly associated with new cases of asthma but SO_2 was not, see Paper 8. In order to determine if the observed association between new cases of asthma and SO_4 might be due to a surrogate relationship with these other pollutants, ambient mean concentrations of first SO_4 and TSP, and then SO_4 and ozone were allowed to compete for entry in the multiple logistic regression models after the covariates of the SO_4 model had been forced in. The covariate, "possible symptoms in 1977" was excluded from these analyses. SO_4 entered the model in preference to both TSP and ozone. Once SO_4 was in the model, the other pollutant failed to make a significant additional contribution to the model. These findings suggest that neither TSP, ozone, nor SO_2 is serving as a surrogate for SO_4 and that SO_4 mean concentration does appear to be related to development of new cases of asthma. The correlations of 1977-1987 mean concentrations of SO_4 between SO_2, ozone and TSP were 0.59, 0.51, and 0.66 respectively.

When "possible symptoms in 1977" is not included as a covariate in the model, SO_4 is the most strongly related pollutant to development of new cases of asthma. However, when "possible symptoms in 1977" was included in the model and ozone, TSP, and SO_4 mean concentration were allowed to compete for entry after the other covariates had been forced in, ozone entered in preference to SO_4 or TSP. Once ozone was in the model, SO_4 and TSP failed to make statistically significant contributions. Thus, which pollutant is most related to development of new cases of asthma depends on whether or not the "possible symptoms in 1977" covariate is included in the model. When it is included, ozone appears to have the strongest

relationship. When it is not included, SO_4 appears to have the strongest relationship. We have ruled out a relationship with SO_2 but cannot rule out a relationship with TSP or ozone.

To explore the possibility of synergistic relationships of TSP, ozone, and SO_4 with development of new cases of asthma, we explored multiple logistic regression models to which ambient concentrations of these pollutants and interactions of (products of) ambient concentrations of these pollutants were added to determine their explanatory power. The chi square approximation to the test for the maximum likelihood ratio statistic was used to determine if additional terms made significant improvements in the models. There was no evidence of synergistic effects in the multiple logistic regression model (and for any forms of ambient concentration and the way in which these pollutants were measured).

The product of TSP mean concentration and SO_4 mean concentration (1977-1987) was also entered by itself in place of SO_4 mean concentration in the final multiple logistic regression models as an indicator of combined ambient concentration of the two pollutants. This combined product variable showed a statistically significant association with development of new cases of asthma and AOD but not chronic bronchitis. However, the level of statistical significance was not as high as for TSP mean concentration (1977-1987) for AOD nor as high as either TSP or SO_4 for asthma. Since the correlation of the product variable with TSP mean concentration was 0.95 and was 0.85 with SO_4 mean concentration, it is likely that the product variable achieved statistically significant association by acting as a surrogate indicator for TSP.

Table 7.3 *Table 3 of Paper 9* summarizes the results of the multipollutant analyses for development of new cases of asthma. A similar analysis for change in symptoms severity score of AOD involving multiple linear regressions showed no evidence of synergistic effects of TSP and SO_4. When TSP is used as the only ambient air pollutant variable in a model, it is a measure of combined concentration of SO_4 particles and other particles, since SO_4 is a component of TSP.

§ 7.6 Other Chronic Disease Outcomes

Tests of association between cancer incidence and levels of ambient SO_4 were not made because SO_4 was not monitored on a statewide basis prior to 1977, but only for the time period 1977 through 1987. Since cancer incidence data was collected only for the time period 1977 through 1982, it was felt that insufficient lag time existed to allow development of cancer to be associated with SO_4.

Tests of association between ambient levels of SO_4 and three other disease outcomes were made. These three disease outcomes included all natural cause mortality (ICD9 000-799), all respiratory disease related mortality (ICD9 160-165; 480-496), and incidence of myocardial infarction. No statistically significant associations were seen between ambient concentrations of SO_4 and these disease outcomes; however, a trend association between incidence of myocardial infarction and the lowest threshold of 6 $\mu g/m^3$ of SO_4 was observed. The relative

risk for myocardial infarction associated with an increase of 1,000 hours in excess of this threshold was 1.17 (95% confidence interval 1.00, 1.37). For 1,000 hours in access of 9 $\mu g/m^3$ the relative risk remained the same, and for 12 $\mu g/m^3$ the relative risk climbed only to 1.22 (95% confidence intervals 0.93, 1.61). This failure of relative risks to increase for the same hours in excess of higher thresholds demonstrated a lack of dose response. Table 7.4 *Table 4 of Paper 11*, gives the regression coefficients and shows the covariates that were included in each multivariate model.

§ 7.7 Sensitivity Analyses

Sensitivity analyses involving adjusted mean concentration of SO_4 to reflect time spent indoors were conducted. Also, interpolations were restricted to those within A or B quality, this resulted in reducing the number of individuals available for analyses by 50%. Results concurred with those described above.

Table 7.1 ***Table 2 of Paper 9***
Multiple Logistic Regression for New Cases of Definite Symptoms of Asthma, 1977-1987, with Mean Concentration of SO_4 as the Air Pollution Exposure Variable.
(n = 3296, cases = 75)

Variable	Regression Coefficient	Increment[a]	Relative Risk[d]	95% C.I. for Relative Risk
SO_4 Mean Concentration[b]	0.15520*	7 $\mu g/m^3$	2.87	1.03, 7.55
Years Worked with Smoker[c]	0.11331**	10 years	2.99	1.59, 5.51
AOD before age 16	1.4847***	(0 = N 1 = Y)	4.16	2.46, 6.87
Gender	-0.14036	(0 = F, 1 = M)	0.87	0.53, 1.42
Age	-0.010845	10 years	0.90	0.74, 1.10
Education	0.017221	4 years	1.07	0.75, 1.52
Constant	-4.7309			

[a] Increment for computations of relative risks.

[b] Average annual mean concentration in $\mu g/m^3$, 1977-1987.

[c] Years worked with smoker 1977 through 1987.

[d] Relative risk of increase of one increment, holding other variables in model constant.

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

Table 7.2 Linear Regression Models for Changes in Symptoms Scores

	SO_4 - Average Hours Exposure Per Year In Excess of 6 $\mu g/m^3$, 1977-1987.					
	AOD (N = 3,346)		Chronic Bronchitis (N = 3,362)		Asthma (N = 3,378)	
Variable	Entry Order	Standardized Reg. Coeff[1]	Entry Order	Standardized Reg. Coeff[2]	Entry Order	Standardized Reg. Coeff[3]
1977 Symptoms Score	1	-0.27	1	-0.50	5	-0.04
Childhood Colds	4	0.06	3	0.08	4	0.05
AOD Before Age 16	2	0.09	7	0.03	2	0.08
Years Smoked in past	3	0.07	2	0.06	No[6]	
Age	7	0.06	4	0.07	8	-0.01
Years Worked with Smoker	8[5]	0.06	No	0.03	1[5]	0.09
Years Dust Exposure at Work	5[4]	0.08	5[4]	0.06	No[6]	
Gender (0=female, 1=male)	6	-0.06	8	-0.03	3	-0.05
SO_4 6 $\mu g/m^3$ [7]	10	0.03	9	0.02	6	0.03
Living with Smoker	9[8]	0.03	6[4]	0.04	No[6]	
Education (Yrs.)	11	-0.01	10	-0.00	7	-0.02
Achieved R^2		0.09		0.25		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 and SO_4.
(3) All regression coefficients were statistically significant ($p<.05$) except for age and education and SO_4.
(4) Total years through 1977.
(5) Total years through 1987.
(6) Did not enter.
(7) Average 1977-1987.
(8) Presently living with smoker in 1987 (0 = no, 1 = yes)

Table 7.3 ***Table 3 of Paper 9***
Results of Multipollutant Analyses on the AHSMOG Cohort for Development of New Cases of Respiratory Symptoms Complexes.

Pollutants	Respiratory Health Effects Associations
Ozone	Asthma [1]
SO_2	None
NO_2	None
TSP	Asthma [1], Chronic Bronchitis [1], AOD [1]
SO_4	Asthma [1]
SO_4 × TSP	Asthma [2], AOD [2]
SO_4 × Ozone	None
TSP × Ozone	None

[1] Association not due to surrogate relationship with other pollutants on table.

[2] May be due to surrogate relationship with TSP.

Table 7.4 ***Table 4 of Paper 11***

Logistic Regression Analysis of SO_4 (1977-1982) as Related To All Natural Cause Mortality (1977-1986) and Definite Myocardial Infarction (1977-1982) and Respiratory Disease Mortality, (1977-1986).

SO_4 Average Hours In Excess of:	Definite M.I.[a]			All Natural Cause Mortality[b]			Respiratory Disease Mortality[c]		
	ß	S.E. (ß)	ß/SE(ß)	ß	S.E. (ß)	ß/SE(ß)	ß	S.E. (ß)	ß/SE(ß)
6 $\mu g/m^3$	$0.16 \cdot 10^{-3}$	$0.80 \cdot 10^{-4}$	1.98	$-0.19 \cdot 10^{-4}$	$0.22 \cdot 10^{-4}$	-0.87	$-0.27 \cdot 10^{-4}$	$0.47 \cdot 10^{-4}$	-0.57
9 $\mu g/m^3$	$0.16 \cdot 10^{-3}$	$0.99 \cdot 10^{-4}$	1.65	$-0.81 \cdot 10^{-5}$	$0.29 \cdot 10^{-4}$	-0.28	$-0.20 \cdot 10^{-4}$	$0.64 \cdot 10^{-4}$	-0.30
12 $\mu g/m^3$	$0.20 \cdot 10^{-3}$	$0.14 \cdot 10^{-3}$	1.43	$0.16 \cdot 10^{-4}$	$0.43 \cdot 10^{-4}$	0.37	$0.17 \cdot 10^{-4}$	$0.95 \cdot 10^{-4}$	0.18
15 $\mu g/m^3$	$0.23 \cdot 10^{-3}$	$0.20 \cdot 10^{-3}$	1.11	$0.50 \cdot 10^{-4}$	$0.64 \cdot 10^{-4}$	0.78	$0.50 \cdot 10^{-4}$	$0.14 \cdot 10^{-3}$	0.35
SO_4 Mean Concentration	$0.17 \cdot 10^{-2}$	$0.65 \cdot 10^{-2}$	0.26	$0.77 \cdot 10^{-3}$	$0.25 \cdot 10^{-2}$	0.31	$-0.46 \cdot 10^{-5}$	$0.62 \cdot 10^{-5}$	-0.75

[a] Covariates include age, sex, total years smoked, years worked with a smoker, high blood pressure and Quetelet's Index.
[b] Covariates include age, sex, education, total years smoked and years lived with a smoker.
[c] Covariates include age, sex and total years smoked.

Chapter 8

Health Effects of Long-Term Concentrations of NO_2.

§ 8.1. Introduction

The average annual ambient mean concentrations and exceedance frequencies in excess of 5, 15, 20, and 25 pphm, were calculated for NO_2, for the time periods 1966 though March, 1977; 1973 through March 1977; 1973 through March 1987; and April 1977 through March 1987. The distributions of these statistics for the respiratory symptoms cohort of 3,914 individuals are given in Figures 1 through 5 of Paper 10, for the time period 1977 through 1987.

A regression estimation procedure was used to adjust ambient mean concentration estimates, 1977 through 1987, for the 3,914 individuals of the respiratory symptoms cohort, using data collected on building characteristics and individual activity patterns in 1977 and 1987. The regression estimates were formed from a personal exposure study conducted on 650 subjects from Los Angeles and Orange counties (Spengler, et al, 1992). (See also chapter 2, section 5 and Appendix C of this report). The frequency distribution of adjusted mean concentrations for the respiratory symptoms cohort is shown in Figure 6, of Paper 10. Adjusted mean concentrations could not be calculated for the cancer incidence cohort, as the detailed questions on housing characteristics were only included in the 1987 questionnaire. Many members of the cancer incidence cohort were deceased or lost to follow-up by this time.

§ 8.2 Respiratory Health Effects

The same steps in model formation as outlined for ozone in Chapter 5, were used. No statistically significant associations were seen between any of the respiratory health outcomes studies and ambient mean concentrations, adjusted ambient mean concentrations, or exceedance frequencies above any cut-offs for NO_2. However, a strong positive trend between unadjusted mean concentration of NO_2 and increasing severity of symptoms for AOD was noted ($p=.05$), as was a positive trend between adjusted NO_2 and increasing severity of AOD symptoms ($p=.14$). The multiple logistic regression models for the various respiratory symptoms outcomes are given in Tables 8.1 through 8.4 *Tables 6 through 9 of Paper 10.* The multiple linear regression models for change in symptoms severity scores are given in Table 8.5.

§ 8.3. Other Chronic Disease Outcomes.

Possible associations between ambient concentrations of NO_2 and incidence of all malignant neoplasms in males, incidence of all malignant neoplasms in females, smoking related respiratory cancers, incidence of myocardial infarction, and all natural cause mortality were assessed using statistical methods similar to those used to investigate associations with ozone.

No statistically significant associations between NO_2 and any of these outcomes were observed. In addition, there was no evidence of increasing risk of health effects (as indicated by larger regression coefficients) with the higher cut-offs of ambient NO_2. The relationship between adjusted ambient concentrations and these outcomes could not be evaluated since adjusted ambient concentrations could not be computed for the entire cohort, but only for those individuals completing the 1987 questionnaire.

§ 8.4. Multipollutant Analyses

Because we saw no statistically significant relationships between NO_2 and the health outcomes, we did not pursue a multipollutant analysis. The correlation coefficients for ambient mean concentrations of NO_2, 1977 - 1987, for the respiratory symptoms cohort with ambient mean concentrations for the other pollutants for this time period are given in Table 12.1.

Table 8.1 ***Table 6 of Paper 10***
Multiple Logistic Regression Coefficients for New Cases of Definite Symptoms of AOD, 1977-1987, with Adjusted Mean Concentration of NO_2 as the Air Pollution Exposure Variable.

(n = 1831, cases = 139)

Variable	Regression Coefficient	Increment[a]	Relative Risk[b]	95% C.I. for Relative Risk
NO_2 Mean Concentration[c]	0.0533370	5 pphm	1.26	0.58, 4.33
Years Smoked in Past	0.0188120	10 years	1.19	0.95, 1.61
Years Lived with Smoker Thru 1977	0.0095866	10 years	1.09	0.95, 1.31
Possible Symptoms in 1977	1.1934***	(0=No, 1=Yes)	2.75	2.03, 3.63
Childhood AOD	0.78101**	(0=No, 1=Yes)	2.00	1.25, 3.09
Childhood Colds	0.28148*	1	1.30	1.06, 1.71
Age	-0.014236	10 years	0.88	0.76, 1.02
Gender	0.29992	(0=F, 1=M)	1.31	0.92, 1.85
Education	0.0110800	4 years	1.04	0.81, 1.44
Constant	-3.3664			

[a] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)

[b] Relative risk of increase in exposure of one increment, holding other variables in model constant.

[c] Average annual adjusted mean concentration in pphm, 1977-1987.

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

Table 8.2 ***Table 7 of Paper 10***
Multiple Logistic Regression Coefficients for New Cases of Definite Symptoms of Bronchitis, 1977-1987, with Adjusted Mean Concentration of NO_2 as the Air Pollution Exposure Variable.

(n = 1880, cases = 119)

Variable	Regression Coefficient	Increment[a]	Relative Risk[b]	95% C.I. for Relative Risk
NO_2 Mean Concentration[c]	-0.0460790	5 pphm	0.81	0.34, 1.82
Years Smoked in Past	0.0250340*	10 years	1.26	1.01, 1.56
Years Lived with Smoker Thru 1977	0.0086189	10 years	1.08	0.93, 1.25
Possible Symptoms in 1977	1.0671***	(0=No, 1=Yes)	2.55	1.81, 3.51
Childhood Colds	0.4127200***	1	1.47	1.19, 1.81
Age	-0.0058623	10 years	0.95	0.81, 1.11
Gender	0.24474	(0=F, 1=M)	1.25	0.85, 1.83
Education	0.0062676	4 years	1.02	0.78, 1.33
Constant	-3.8638			

[a] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
[b] Relative risk of increase in exposure of one increment, holding other variables in model constant.
[c] Average annual adjusted mean concentration in pphm, 1977-1987.

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

Table 8.3 ***Table 8 of Paper 10***
Multiple Logistic Regression Coefficients for New Cases of Definite Symptoms of Asthma, 1977-1987, with Adjusted Mean Concentration of NO_2 as the Air Pollution Exposure Variable.

(n = 2061, cases = 46)

Variable	Regression Coefficient	Increment[a]	Relative Risk[b]	95% C.I. for Relative Risk
NO_2 Mean Concentration[c]	0.19866	5 pphm	2.48	0.59, 7.91
Possible Symptoms in 1977	3.7703***	(0=No, 1=Yes)	22.45	12.51, 32.50
Years Worked with a Smoker thru 1987	0.044578***	10 years	1.55	1.21, 1.98
Age	-0.023488	10 years	0.80	0.61, 1.03
Gender	-0.53743	(0=F, 1=M)	0.59	0.30, 1.17
Education	0.059773	4 years	1.26	0.77, 2.04
Constant	-4.3949			

[a] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
[b] Relative risk of increase in exposure of one increment, holding other variables in model constant.
[c] Average annual adjusted mean concentration in pphm, 1977-1987.

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

Table 8.4 ***Table 9 of Paper 10***
Multiple Logistic Regression Coefficients for New Cases of Definite Symptoms of "Doctor Told" Asthma, 1977-1987, with Adjusted Mean Concentration of NO_2 as the Exposure Variable.

(n = 2060, cases = 47)

Variable	Regression Coefficient	Increment[a]	Relative Risk[b]	95% C.I. for Relative Risk
NO_2 Mean Concentration[c]	-0.052699	5 pphm	0.78	0.19, 2.88
Childhood AOD	1.4405	(0=No, 1=Yes)	3.99	2.03, 7.58
Years Worked with a Smoker thru 1987	0.038542**	10 years	1.46	1.14, 1.87
Age	-0.027851*	10 years	0.76	0.59, 0.98
Gender	-0.82432*	(0=F, 1=M)	0.44	0.22, 0.89
Education	0.092564	4 years	1.43	0.89, 2.28
Constant	-3.6299			

[a] Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
[b] Relative risk of increase in exposure of one increment, holding other variables in model constant.
[c] Average annual adjusted mean concentration in pphm, 1977-1987.

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

Table 8.5 Linear Regression Models for Change in Symptoms Scores Based on Unadjusted Mean Concentration of NO_2

	AOD N = 3474		BRONCHITIS N = 3531		ASTHMA N = 3895	
Variable Name	**Entry Order**	**Std Coeff[2]**	**Entry Order**	**Std Coeff[3]**	**Entry Order**	**Std Coeff[4]**
Unadjusted Mean Conc. of NO_2 [1]	10	0.022[ns]	9	-0.008[ns]	7	0.009[ns]
Years Smoked Through 03/01/77 (1977)	6	0.055[b]	3	0.060[c]	-	-
Years Lived with Smoker Through 03/01/77 (1977)	8	0.037[a]	6	0.047[b]	-	-
Years Worked with Smoker Through 03/01/77 (1987)	4	0.061[c]	-	-	1	0.087[e]
Years Exposed to Dust Through 03/01/77 (1977)	5	0.065[c]	4	0.053[c]	-	-
AOD Symptoms Before Age 16 Years	2	0.092[c]	-	-	2	0.086[e]
Frequency of Childhood Colds	3	0.080[e]	2	0.087[e]	-	-
1977 Symptom Score	1	-0.274[e]	1	-0.486[e]	3	-0.044[b]
Age in 1977	9	0.058[c]	5	0.079[e]	5	-0.011[ns]
Gender (0 = male, 1 = female)	11	-0.055[b]	8	-0.023[ns]	4	-0.045[b]
Years of Education in 1993	7	-0.006[ns]	7	-0.002[ns]	6	-0.012[ns]

(1) 1977-1987 for AOD, Asthma; 1973-1977 for Bronchitis.
(2) All regression coefficients were statistically significant ($p < .05$) except NO_2 ($z = 1.95$) and education.
(3) All regression coefficients were statistically significant ($p < .05$) except NO_2, gender, and education.
(4) All regression coefficients were significant ($p < .05$) except NO_2, age, and education.
[a] $< .05$
[b] $< .01$
[c] $< .001$
[d] $< .0001$
[e] $< .00001$
[ns] not statistically significant

Chapter 9

Health Effects Associated with Estimated Long-Term Ambient Concentrations of PM10.

This chapter summarizes results reported in Papers 15 and 16.

§ 9.1 Estimating Ambient Concentrations

PM10 has been monitored widely throughout California, only since 1985. In order to estimate ambient concentrations of PM10 for study participants for years prior to 1985, site and seasonal specific regression equations of PM10 on TSP were formed using paired data, i.e., data where simultaneous measures of PM10 and TSP existed throughout the state of California, between the years 1982 and 1989. These regression equations were then applied to monitored TSP data from 1973 through 1987 to produce estimated long-term concentrations of PM10 for study participants (see Appendix E).

The covariates used for the health effects regression models were the same as those selected according to stepwise selection procedures for TSP. This was done because of the high correlation, R = 0.97, that existed between (1973-1987) cumulated ambient mean concentrations of indirectly estimated PM10 and TSP for study participants. Although the covariates for the PM10 models were chosen to be the same as for TSP, for covariates which represented a time period, such as 1973 through 1977, and 1977 through 1987, the stepwise process was allowed to select possibly different time periods than those for TSP. The covariates are listed in Table 3.3 *Table 1 of Paper 8.*

Exceedance frequency and excess concentrations for cut-offs 40, 50, 60, 80, and 100 $\mu g/m^3$ were computed. The frequency distributions for the exceedance frequency statistics as well as ambient mean and adjusted ambient mean concentration are given for the respiratory symptoms cohort in Figures 20 through 24 of Appendix F and for the Cancer Incidence Cohort in Figures 1 through 6 of Paper 16. An adjustment factor of 0.7 obtained from Winer (1989) was applied to each individual's estimated monthly mean concentration according to the estimated time spent indoors that month.

§ 9.2 Development of AOD

The multiple logistic regression models for development of new cases of definite symptoms of AOD between 1977 and 1987 as associated with ambient concentrations of PM10 above 100 $\mu g/m^3$, 1973-1977 are given in Table 9.1 *Table 3 of Paper 15.* Exceedance frequencies in excess of 80 and 100 $\mu g/m^3$ were significantly associated with development of AOD. Excess concentrations statistics in excess of all cutoffs were statistically significantly related to development of new cases of AOD. Neither mean concentration nor adjusted mean concentration of PM10 were significantly related to development of AOD.

Table 9.4 *Table 6 of Paper 15* shows the estimated increased relative risk for various increments of time in excess of various cutoffs. A 1,000 hour-per-year (42 day per year) increase in ambient concentrations above 100 $\mu g/m^3$, was associated with a 17% increased relative risk of developing AOD between 1977 and 1987. Figure 1 of Paper 15 plots relative risk of developing AOD for various increments of exceedance frequencies above different cutoff levels. Figure 2 shows relative risk contour plots for development of new cases of AOD as related to different cutoff levels of PM10.

§ 9.3 Development of Chronic Bronchitis

New cases of definite chronic bronchitis symptoms were statistically significantly related to estimated long-term ambient concentrations of PM10. Table 9.2 *Table 4 of Paper 15* gives a multiple logistic regression model relating estimated average annual hours of concentrations of PM10 in excess of 100 $\mu g/m^3$ with development of chronic bronchitis. An increment of 1,000 hours-per-year (42 days per year) was statistically significantly ($p < .05$) associated with a 17% increased relative risk for development of chronic bronchitis symptoms. Exceedance frequencies for cutoffs lower than 100 $\mu g/m^3$ were not significantly related to development of chronic bronchitis. Neither estimated ambient mean concentration nor adjusted ambient mean concentration of PM10 was significantly related to development of chronic bronchitis. Excess concentrations statistics for all cutoffs were significantly related to development of chronic bronchitis. The relative risks associated with various increments above the different cutoffs are given in Table 9.4 *Table 6 of Paper 15*. The time period of ambient concentrations of PM10 showing the most significant relationship with chronic bronchitis was 1/1/73 through 3/31/77.

§ 9.4 Development of Asthma

The multiple logistic regression model for development of new cases of asthma between 1977 and 1987, as related to long-term estimated ambient concentrations of PM10 is given in Table 9.3 *Table 5 of Paper 15*. None of the exceedance frequencies or excess concentration statistics for any of the cutoffs were related to development of asthma, nor were estimated ambient mean concentrations or adjusted estimated mean concentrations. The time period of ambient concentrations of estimated PM10 which was most related to development of asthma was 4/1/77 through 3/31/87. Table 9.4 *Table 6 of Paper 15* gives relative risk for various increments above the different cutoff levels. Relative risks for a fixed increment of ambient concentration increase for increasing cutoff levels indicating a dose response relationship. This is true for AOD and chronic bronchitis also.

§ 9.5 Change in Respiratory Symptoms Severity Scores

Multiple linear regression models related change in respiratory symptoms severity score 1977-1987, for each of the respiratory symptoms complexes to the various exceedance frequency

and excess concentration statistics of PM10. The models for PM10 (100) are given in Table 9.5. The regression coefficients for exceedance frequency statistics above all cutoffs were statistically significant ($p<.05$) for change in severity of AOD. For chronic bronchitis, exceedance frequency statistics were not significant for any of the cutoffs for any of the cutoffs. For asthma, regression coefficients for exceedance frequency statistics for cutoffs of 50 $\mu g/m^3$ and higher were significantly related to increasing severity of symptoms. The magnitude of the regression coefficients for all diseases increased and their tail probabilities decreased with increasing cutoff levels, indicating that a consistent dose-response type of relationship existed. Mean concentration was statistically significant ($p<.05$) for AOD and asthma but not for chronic bronchitis. For excess concentration, multiple linear regression models showed statistically significant associations ($p<.01$) at all cutoff levels for both AOD and asthma. A dose-response relationship was also apparent, since the magnitudes of the regression coefficients increased with the cutoffs.

§ 9.6 Sensitivity Analyses for Respiratory Health Outcomes

An adjustment factor of 0.7 obtained from Winer (1989), was applied to each individual's estimated monthly mean concentration according to the estimated time spent indoors that month. The multiple logistic and linear regression models were rerun using adjusted mean concentration of PM10. The statistical significance remained very similar to models using unadjusted mean concentration of PM10, however, the magnitudes of the regression coefficients increased somewhat in proportion to the decreased range of the adjusted mean concentrations.

To determine the impact of interpolation error on our analyses, a sensitivity analysis was conducted where we restricted interpolations to be within the A or B quality range and re-ran the final regression models for PM10 (100). This reduced the number of individuals available for analyses by 30%. For AOD, the magnitude of the logistic regression coefficient was reduced slightly (4%) and the z value dropped from 2.2 to 1.8, failing to reach statistical significance. For chronic bronchitis, the magnitude of the logistic regression coefficient increased slightly (13%) and its z value was essentially unchanged ($z=2.1$). For asthma the magnitude of the logistic coefficient dropped by 46% and the z value dropped from 1.8 to 0.9 (51%). T-tests indicated that ambient concentrations of PM10 were statistically significantly higher for individuals who were within the A or B quality interpolation ranges (average annual ambient concentration 1977-1987 of 53.5 $\mu g/m^3$) than for those who lived outside these ranges (average annual concentration of 38.7 $\mu g/m^3$), ($p<.0001$). Thus restricting analyses to A or B quality is omitting individuals with the lowest ambient concentrations and it may be biasing analyses towards the null hypothesis.

Sensitivity analyses were conducted for development of definite symptoms of AOD, chronic bronchitis, and asthma, deleting the covariate "possible symptoms in 1977" from the models for PM10(100). Results concurred with those given above. Similarly the analyses for change in symptoms severity score were conducted excluding the 1977 symptoms severity score from the models for PM10(100). For AOD and chronic bronchitis results were no longer

statistically significant whereas for change in asthma severity results concurred with those given above.

§ 9.7 Health Effects Results for Other Chronic Disease Outcomes

During the period of follow-up for cancer incidence (1977-1982), there were 292 cases of cancer diagnosed among study participants (113 male;179 female). During this same time period there were 63 cases of newly diagnosed myocardial infarction. In addition, during the mortality follow-up period which extended through 1986, there were 275 deaths from cardiovascular disease, 47 deaths from respiratory disease and 848 deaths from all natural causes. Only 17 newly diagnosed cases of respiratory cancer were observed.

Cox proportional hazards regressions adjusting for covariates indicated no significant associations between either exceedance frequencies of PM10 above any cutoff or mean concentrations and cancer incidence in males, respiratory disease mortality, cardiovascular disease mortality or all natural cause mortality. For myocardial infarction, there was only a slight, non-significant elevation in the relative risk for the lowest cutoff level of 40 $\mu g/m^3$ (R.R.=1.52; 95% C.I· 0.96, 2.41) and there was no evidence of increasing risk with increasing concentration of PM10.

However, for cancer among the female members of the cohort and respiratory cancer, suggestive positive associations were observed, see Table 9.6 *Table 1 of Paper 16*. Although none of the relative risk estimates were statistically significant (i.e. all 95% confidence intervals included the null value) there was evidence of dose-response patterns in that higher risk estimates were observed for estimated ambient concentrations in excess of the higher cutoff levels of PM10. For the disease outcome, cancer incidence in females, for example, for a constant number of days per year (e.g. 125 days/yr) in excess of several concentration levels of PM10, the relative risk estimates were 1.13, 1.19, 1.24, 1.32 and 1.54 for 40, 50, 60 80 and 100 $\mu g/m^3$ respectively. (These results were derived from the Cox regression model run separately for each successive cutoff of PM10 treating exceedance frequencies above the cutoff as a continuous variable.)

When the levels of PM10 mean concentration were categorized into tertiles and a stratified Mantel-Haenszel approach was utilized a similar dose response relationship was observed. In Table 9.7 *Table 2 of Paper 16* increasing levels of PM10 mean concentration are seen to be associated with slight, though non-significant, increases in the relative risks for cancer incidence in females. The trend test was also of borderline statistical significance (p=0.043).

For respiratory cancer, similar elevated patterns were observed although the point estimates themselves were somewhat larger. For 125 days per year in excess of 100 $\mu g/m^3$, for example, the relative risk estimate was 3.09 for respiratory cancer. Because this finding was based on such small numbers, however, the confidence interval was large and included the null value.

§ 9.8 Sensitivity Analyses for Other Health Outcomes

Sensitivity analyses were conducted for adjusted mean concentration which adjusted ambient mean concentration for time spent indoors and restricting the cohort to those for whom 80% of their residence months were in zip codes with A or B quality interpolations. Results were consistent to those described above.

Table 9.1 *Table 3 of Paper 15*
Multiple Logistic Regression for New Cases of Definite Symptoms of AOD in 1987 with Average Annual Hours of Concentrations in Excess of 100 $\mu g/m^3$ of PM10 as the Air Pollution Variable.

(n = 3236, cases = 275)

Variable	Regression Coefficient	Increment§	Relative Risk//	95% C.I. for Relative Risk
PM10 (Hrs. in Excess of 100 $\mu g/m^3$)#	0.00016993*	1000 hr/yr.	1.17	1.02, 1.33
Years smoked	0.021522*	10 yr.	1.22	1.04, 1.42
Years Lived with Smoker**	0.012338*	10 yr.	1.12	1.02, 1.23
Years Worked with Smoker††	0.013475*	10 yr.	1.13	1.01, 1.27
Possible Symptoms in 1977	1.2931‡	(0 = No, 1 = Yes)	2.97	2.41, 3.60
Childhood AOD	0.56765†	(0 = No, 1 = Yes)	1.66	1.15, 2.33
Childhood Colds	0.24093†	1	1.25	1.08, 1.44
Gender	0.17161	(0 = F, 1 = M)	1.17	0.90, 1.52
Age	-0.0012603	10 yr.	0.99	0.89, 1.09
Education	0.013011	4 yr.	1.05	0.88, 1.25
Constant	-3.9333			

§ Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
// Relative risk of increase in exposure of one increment, holding other variables in model constant.
Average annual hours in excess of 100 $\mu g/m^3$ 1973-1977.
** Years lived with smoker through 1977.
†† Years worked with smoker through 1987.

* $p < .05$; † $p < .01$; ‡ $p < .001$.

Table 9.2 ***Table 4 of Paper 15***
Multiple Logistic Regression for Development of New Cases of Definite Chronic Bronchitis Symptoms in 1987 with Average Annual Hours of Concentrations in Excess of 100 $\mu g/m^3$ of PM10 as the Air Pollution Variable.

(n = 3327, cases = 239)

Variable	Regression Coefficient	Increment§	Relative Risk//	95% C.I. For Relative Risk
PM10 (Hrs. in Excess of 100 $\mu g/m^3$)#	0.00017065*	1000 hr/yr.	1.17	1.01, 1.35
Years smoked	0.027653†	10 yr.	1.29	1.11, 1.50
Years Lived with Smoker**	0.015299†	10 yr.	1.15	1.05, 1.27
Possible Symptoms in 1977	1.2241‡	(0 = No, 1 = Yes)	2.89	2.30, 3.60
Childhood Colds	0.31898‡	(0 = No, 1 = Yes)	1.35	1.16, 1.57
Gender	0.32236*	(0 = F, 1 = M)	1.35	1.02, 1.76
Age	0.0037632	10 yr.	1.04	0.93, 1.16
Education	0.012772	4 yr.	1.05	0.87, 1.26
Constant	-4.5408			

§ Increment for computations of relative risks. For childhood colds the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)
// Relative risk of increase in exposure of one increment, holding other variables in model constant.
Average annual hours in excess of 100 $\mu g/m^3$ 1973-1977.
** Years lived with smoker through 1977.

* $p < .05$; † $p < .01$; ‡ $p < .001$.

Table 9.3 ***Table 5 of Paper 15***
Multiple Logistic Regression for New Cases of Definite Symptoms of Asthma with Average Annual Hours of Concentrations in Excess of 100 $\mu g/m^3$ of PM10 as the Air Pollution Variable.

(n = 3634, cases = 79)

Variable	Regression Coefficient	Increment§	Relative Risk//	95% C.I. for Relative Risk
PM10 (Hrs. in Excess of 100 $\mu g/m^3$)#	0.00026761	1000 hr/yr.	1.30	0.97, 1.73
Years worked with Smoker**	0.040445‡	10 yr.	1.49	1.22, 1.81
Possible Symptoms in 1977	4.0471‡	(0 = no, 1 = yes)	24.96	17.64, 31.60
Gender	-0.60760*	(0 = F, 1 = M)	0.55	0.32, 0.94
Age	-0.015771	10 yr.	0.86	0.71, 1.04
Education	0.034216	4 yr.	1.14	0.78, 1.67
Constant	-4.0235			

§ Increment for computations of relative risks.
// Relative risk of increase in exposure of one increment, holding other variables in model constant.
Average annual hours in excess of 100 $\mu g/m^3$ 1977-1987.
** Years worked with smoker through 1987.

* $p < .05$; † $p < .01$; ‡ $p < .001$.

able 9.4 *Table 6 of Paper 15*
Estimates of Relative Risk for Definite Symptoms of AOD, Chronic Bronchitis, and Asthma from Multiple Logistic Regression for Different Incremental Increases of Amount of Time Ambient Concentrations Exceeded Various Cutoff Levels of PM10.

Cutoff Level	Increment† in Hours Per Year	Increment† Days Per Year	Percent Population Exposed	Relative Risk Estimate		
				AOD	Chronic Bronchitis	Asthma
40 $\mu g/m^3$	250	10.4	100	1.01	1.01	1.02
	500	20.8	100	1.03	1.02	1.04
	1000	41.6	99	1.05	1.04	1.08
	2500	104.0	84	1.13	1.11	1.22
	5000	208.0	56	1.28	1.24	1.49
50 $\mu g/m^3$	250	10.4	99	1.01	1.01	1.02
	500	20.8	98	1.03	1.02	1.05
	1000	41.6	92	1.06	1.05	1.10
	2500	104.0	67	1.14	1.13	1.28
	5000	208.0	39	1.31	1.27	1.63
60 $\mu g/m^3$	250	10.4	98	1.02	1.02	1.03
	500	20.8	94	1.03	1.03	1.06
	1000	41.6	79	1.07	1.06	1.13
	2500	104.0	53	1.18	1.16	1.35
	5000	208.0	14	1.38	1.34	1.83
80 $\mu g/m^3$	250	10.4	82	1.02*	1.02	1.04
	500	20.8	68	1.05*	1.05	1.08
	1000	41.6	55	1.10*	1.09	1.17
	2500	104.0	22	1.26*	1.25	1.49
100 $\mu g/m^3$	250	10.4	63	1.04*	1.04*	1.07
	500	20.8	46	1.08*	1.08*	1.14
	1000	4.6	25	1.17*	1.17*	1.30
	$\mu g/m^3$					
Mean Concentration	20		98	1.15	1.15	1.27
	30		91	1.23	1.23	1.44
	40		72	1.32	1.32	1.62
	50		53	1.41	1.41	1.82
	60		31	1.51	1.51	2.05
	70		18	1.62	1.62	2.31

† Increment for computations of relative risk. Hours per year 1/1/73 through 3/31/77. Units for mean concentration are $\mu g/m^3$.

* Regression coefficient from which relative risks are calculated is statistically significant ($p < .05$)

Table 9.5 Linear Regression Models for Change in Symptoms Scores.

PM_{10} Average hours exposure per year in excess of 100 $\mu g/m^3$, 1977-1987						
	AOD (N = 3,679)		Chronic Bronchitis (N = 3,699)		Asthma (N = 3,716)	
Variable	Entry Order	Standardized Reg.Coeff.	Entry Order	Standardized Reg.Coeff.	Entry Order	Standardized Reg. Coeff.
1977 Symptoms Score	1	-0.27***	1	-0.50***	5	-0.05**
Childhood Colds	4	0.08***	2	0.08**	4	0.05**
Years Smoked	2	0.07***	4	0.05**	No	
Age	5	0.07***	3	0.08***	8	-0.01
AOD Before age 16	3	0.09***	7	0.03*	2	0.08***
Years Worked with Smoker	8	0.06***	8	0.03*	1	0.09***
Years Dust Exposure at Work	6	0.07***	5	0.06***	No	
Gender (0=female, 1=male)	7	-0.06**	10	-0.02	3	-0.05**
PM10 100 $\mu g/m^3$	9	0.04*	9	0.03	6	0.05**
Years Lived with Smoker	10	0.04*	6	0.04**	No	
Education (yrs)	11	-0.01	11	0.00	7	-0.02
Achieved R^2		0.09		0.25		0.02

*p .05
**p <.01
***p <.001

Table 9.6 *(Table 1 of Paper 16)*
Relative Risks Derived from Cox Proportional Hazards Regression Analysis of Average Annual PM10 (1973-1977) for ıncer Incidence Outcomes. (n=6142)

Cut-off	% Cohort in Excess of Increment	Increment[1] Hrs/yr (Days)	Cancer in Males[2] Relative Risk (95% C.I.)	Cancer in Females[3] Relative Risk (95% C.I.)	Respiratory Cancer[3] Relative Risk (95% C.I.)
40 $\mu g/m^3$	91	2000 (83)	1.05 (.87,1.26)	1.09 (.93,1.27)	1.35 (.77,2.37)
	83	3000 (125)	1.07 (.81,1.42)	1.13 (.89,1.44)	1.57 (.67,3.64)
	78	4000 (167)	1.10 (.75.1.59)	1.18 (.86,1.62)	1.82 (.59,5.60)
	69	5000 (208)	1.12 (.70,1.79)	1.23 (.82,1.83)	2.11 (.52,8.62)
50 $\mu g/m^3$	80	2000 (83)	1.04 (.86,1.26)	1.12 (.96,1.32)	1.43 (.81,2.51)
	71	3000 (125)	1.06 (.80,1.41)	1.19 (.93,1.52)	1.71 (.73,3.97)
	63	4000 (167)	1.09 (.75,1.58)	1.26 (.91,1.74)	2.04 (.66,6.28)
	54	5000 (208)	1.11 (.69,1.78)	1.34 (.89,2.00)	2.44 (.60,9.95)
60 $\mu g/m^3$	81	1000 (42)	1.02 (.91,1.13)	1.07 (.98,1.17)	1.23 (.91,1.66)
	70	2000 (83)	1.03 (.84,1.27)	1.15 (.96,1.38)	1.50 (.82,2.75)
	60	3000 (125)	1.05 (.76,1.44)	1.24 (.94,1.62)	1.85 (.75,4.57)
	47	4000 (167)	1.06 (.70,1.62)	1.33 (.93,1.90)	2.26 (.68,7.57)
	15	5000 (208)			
80 $\mu g/m^3$	64	1000 (42)	1.02 (.88,1.18)	1.10 (.97,1.24)	1.33 (.92,1.93)
	45	2000 (83)	1.04 (.78,1.39)	1.20 (.95,1.53)	1.78 (.85,3.73)
	24	3000 (125)	1.06 (.69,1.63)	1.32 (.92,1.90)	2.37 (.78,7.19)
100 $\mu g/m^3$	29	1000 (42)	1.00 (.80,1.24)	1.15 (.97,1.38)	1.46 (.88, 2.40)
	20	2000 (83)	1.00 (.64,1.54)	1.33 (.94,1.89)	2.12 (.78, 5.78)
Mean Concentration	66	50 $\mu g/m^3$	1.12 (.64,1.98)	1.38 (.84,2.25)	3.54 (.67,18.75)
	23	70 $\mu g/m^3$	1.17 (.53,2.60)	1.57 (.79,3.11)	5.88 (.57,60.55)

(1) Increments are expressed as hours (days) per year above cutoff except for mean concentration where increment is in units of $\mu g/m^3$. Exceedance frequencies were modelled as continuous variables and RR computed for an increase corresponding to stated increment.

(2) Covariates in Cox Proportional Hazards Regression include age, gender, years of education, years smoked in past, employment in occupation with hazardous air pollutants for 1 year or more.
Covariates in Cox Proportional Hazards Regression include age, gender, years of education, years smoked in past.

Table 9.7 ***Table 2 of Paper 16***
Mantel-Haenszel Adjusted* Relative Risks of Mean Concentration of PM10 (1973-1977) Associated with Cancer Incidence in Females

PM10 Mean Concentration Level	Relative Risk (95% C.I.)	No. Cases/No Person-Years
$<50\ \mu g/m^3$	1.00	50/7404
50-64 $\mu g/m^3$	1.24(.86,1.79)	68/8096
$\geq 65\ \mu g/m^3$	1.46(.99,2.14)	61/5697
	Trend p=0.043	

*Adjusted for age, education and total years of past smoking

Chapter 10

Health Effects Associated with Estimated Long-Term Ambient Concentrations of PM2.5.

This chapter summarizes results reported in Papers 12 and 17.

§ 10.1 Methods for Estimating Ambient Concentrations of PM2.5

PM2.5 was not monitored on a consistent statewide basis during the years of this study. Hence, ambient concentrations of PM2.5 were estimated from airport visibility data in the vicinity of 9 airports scattered throughout California for the years 1966 through 1986 using the methods outlined below. Full details of these estimation methods are given in Appendix D.

PM2.5 was monitored at a limited number of sites by the California Air Resources Board during the years 1979-1986. Twenty-four hour average concentrations were monitored every sixth day. PM2.5 monitoring was never part of the CARB's routine monitoring program, and only a limited amount of monitoring was performed at many of the sites which contributed data to this study. Though PM2.5 was not monitored extensively during these years, sufficient data existed to form regression equations which related PM2.5 concentrations to visibility in the vicinities of the nine airports. Table 10.1 *Table 1 of Paper 17* lists the airport areas, the numbers of paired observations of PM2.5 concentrations and visibility, the numbers of subjects living in each area in 1987, and the mean estimated ambient PM2.5 concentrations for the years 1966-1986 and their standard errors. Analyses of area specific PM2.5/visibility data and the geographic distribution of the study population indicated that the Ontario airport area could be subdivided into three sub-areas, and the San Francisco and San Jose airport areas could be combined. Hence this was done.

Estimates of 24-hour mean ambient concentrations of PM2.5 were computed from the regression equations for each airport area for each day of the years 1966-1986 with valid visibility data. Monthly mean concentrations were computed from the daily mean concentrations for the months that had sufficient data to be considered representative. The percentages of days during each month on which mean PM2.5 concentration exceeded three cutoff levels -- 20, 30, and 40 $\mu g/m^3$ -- were also computed. The monthly percentages of days exceeding the cutoffs were converted to hours exceeding the cutoffs for comparability with analogous exceedance frequency statistics for gaseous pollutants.

Ambient mean concentrations of PM2.5 adjusted to reflect time spent indoors were also computed for study participants. Study participants were asked in 1977 and again in 1987 how many hours per week they spent outside of buildings during the months of June through September and the months of October through May. Based on studies of the penetration of ambient PM10 to indoor environments, an adjustment factor of 0.8 (Winer, 1989) was applied to the estimated hours spent indoors each month.

The distribution of subjects' ambient mean PM2.5 concentration for 1966-1986 is given in Figure 2 of Paper 12. These continuous measures of subjects' ambient concentrations were used for most of the health effects analyses. However, because the unadjusted estimated mean concentration of PM2.5 had a tri-modal distribution (see Figure 2 of Paper 12), investigating the risks of the three groups of subjects corresponding to the three modes was also of value. Subjects were classified into three groups according to their average ambient concentration of PM2.5 from 1966-1986 - low, less than 20 $\mu g/m^3$, medium, 20-39 $\mu g/m^3$, and high, 40 $\mu g/m^3$ or greater.

The airport areas were classified into the same groups and the annual mean concentrations of the low, medium, and high groupings were plotted (see figure 6 of Paper 17) to determine if there were time trends. No time trends were apparent except for the only high area, Ontario East. Its annual mean concentrations had a decreasing trend, but remained the highest throughout the 20 years of data. Time plots of individual airport areas (see Figures 1 through 11 of Appendix F) were also examined to determine if their estimated annual mean concentrations of PM2.5 remained within the low, medium, or high range of their group classification over time. All the airport areas except San Jose and Ontario Central stayed within their group's range. Estimated PM2.5 for San Jose gradually increased over the 20-year time period, beginning at the high end of the low range and ending at the low end of the medium range. Annual estimated mean concentrations for Ontario Central started at the low end of the high range and gradually decreased to the high end of the medium range.

Geographic areas surrounding each airport, for which the regression estimates of PM2.5 concentrations were considered representative of ambient concentrations, were identified by the study's epidemiologists and CARB staff with expertise in fine particulate estimation. Zip codes in each of the geographic areas were given A (higher) or B (lower) quality ratings according to how well the regression estimate was thought to represent PM2.5 concentrations at the zip code's centroid.

A subject was not included in the health effects analyses unless at least 80% of his/her months of residence during 1966-1986 satisfied two criteria: (1) the subject was residing in one of the airport areas and (2) the month had representative data. Application of these criteria reduced the original cancer incidence cohort from 6,340 to 3,627 individuals and the respiratory symptoms cohort from 3,914 individuals to 1,868. These subjects are referred to as the "airport subcohorts" in subsequent chapters.

The subjects' estimated monthly PM2.5 mean concentrations and exceedance frequency statistics were cumulated over 1966-86 according to their zip code by month residence histories. Subjects' air pollution values in the statistical models were the long-term averages of these cumulated statistics. Missing months were assigned the average value for the time period.

Distributions of ambient mean concentrations, adjusted ambient mean concentration and exceedance frequencies for each of the cutoffs 20, 30, and 40 $\mu g/m^3$ are given for members of

the respiratory symptoms cohort in Figures 1 through 5 of Paper 17 and for the cancer incidence cohort in Figures 1 through 6 of Paper 12.

§ 10.2 Development of Respiratory Symptoms

Long-term estimated ambient concentrations of PM2.5 were not statistically significantly related to development of AOD or asthma, although an elevated relative risk of 1.46 (95% confidence intervals (C.I.) for AOD and 1.41 (C.I. 0.47, 4.06)for asthma was associated with a 45 $\mu g/m^3$ increase in mean concentration. Lack of statistical significance may be due to lack of power because of increased measurement error for the indirect estimates of PM2.5 and the reduced sample size of the airport subcohort. For development of chronic bronchitis only exceedance frequencies for the 20 $\mu g/m^3$ cutoff were significantly related. Neither ambient mean concentration, adjusted mean concentration, nor exceedance frequencies for the 30 and 40 $\mu g/m^3$ cutoffs were significantly related to development of chronic bronchitis. An increment of 4,000 hours-per-year (167 days per year) in concentrations exceeding the 20 $\mu g/m^3$ cutoff was associated with a 41% increased relative risk for development of chronic bronchitis. These relative risks do not increase for the higher cutoffs; the same increments above 30 $\mu g/m^3$ and 40 $\mu g/m^3$ had, respectively, a lower relative risk and the same relative risk as the increment above 20 $\mu g/m^3$. The time period of estimated PM2.5 which was most related to development of chronic bronchitis was 1966 through March, 1977. The relative risk for increments above each of the cutoff levels, as well as mean concentration, are given in Table 10.5 *Table 5 of Paper 17.* Multiple logistic regression models for each of AOD, chronic bronchitis, and asthma are given in Tables 10.2, 10.3, and 10.4 *Tables 2, 3, and 4 of Paper 17.*

§ 10.3 Change in Respiratory Symptoms Severity Scores

Ambient mean concentration of PM2.5 was significantly associated with change in severity score for AOD, chronic bronchitis, and asthma. Table 10.6 *Table 6 of Paper 17* gives the standardized regression coefficients for PM2.5 mean concentration and each of the other covariates in the multiple linear regression model along with their entry order. The standardized regression coefficients can be used to compare the magnitude of the effects of the different variables on change in symptoms severity score. The time period of ambient PM2.5 mean concentration which was most related to development of AOD and chronic bronchitis was 1977-1987; the time period most related to development of asthma was 1966-1977.

The linear regression models were repeated for exceedance frequencies for each of the cutoffs 20, 30, and 40 $\mu g/m^3$. For change in severity score of AOD the regression coefficients for exceedance frequency for each of these cutoffs was statistically significant ($p < 0.05$). For change in severity of chronic bronchitis the regression coefficient was statistically significant only for the cutoff 20 $\mu g/m^3$. For change in severity of asthma the regression coefficient was significant only for the cutoff 40 $\mu g/m^3$. The magnitude of the non-standardized regression

coefficients increased with increasing cutoff levels for each of change in severity of AOD, chronic bronchitis, and asthma indicating a dose response type of relationship.

§ 10.4 Sensitivity Analyses for Respiratory Symptoms Outcomes

Using an indoor infiltration factor of 0.8 obtained from Winer (1989), and estimates by season of time spent indoors obtained from study participants in 1977 and 1987, adjusted estimates of ambient mean concentration for study participants were formed. For the multiple logistic regressions used for development of AOD, chronic bronchitis, and asthma the regression coefficients for adjusted mean concentration were larger than that for unadjusted corresponding to a decreased range in estimated mean concentration. The levels of statistical significance for the regression coefficients remained essentially unchanged. For the multiple linear regressions used for change in symptoms severity score for AOD, chronic bronchitis, and asthma, the standardized regression coefficients remained essentially unchanged with the level of statistical significance or z value decreasing somewhat and becoming non-statistically significant for change in severity of AOD. Cigarette smoke, an important indoor source of PM2.5, has been taken into account as a covariate in the analyses.

In order to address the effect of applying PM2.5 estimates based on airport visibility data to the zip codes of surrounding areas, each of the zip codes in the airport areas was classified as grade A or B by a team of fine particulate experts from Air Resources Board staff. Quality A zip codes were those closest to the airport where it was felt that PM2.5 estimates obtained from airport visibility measures would well represent the PM2.5 concentrations in a zip code area. Quality B zip codes were those farther removed but within what was deemed to be a reasonable distance of application. A sensitivity analysis was conducted where subjects were restricted to those for whom 80% of the residence months between 1966 and 1987 were in zip codes within the A quality range. This reduced the number of subjects available for analyses from 1,868 to 1,372.

The magnitude and level of statistical significance for development of AOD and chronic bronchitis was decreased somewhat for this reduced group of subjects. For development of asthma, the sign of the regression coefficient became negative and remained nonstatistically significant. For change in symptoms severity score, the regression coefficients for mean concentration of PM2.5 were no longer statistically significant. The magnitude of the standardized regression coefficients dropped somewhat for AOD and asthma but remained unchanged for chronic bronchitis. The restriction to A quality data eliminated individuals having lower estimated ambient PM2.5 concentrations. A t-test conducted between those individuals meeting the A quality restriction and those not meeting this restriction indicated that the estimated mean ambient concentration for PM2.5 for those meeting the restriction was 38.3 $\mu g/m^3$ and for those not meeting the restriction 25.0 $\mu g/m^3$ for 1966 through 1977. A t-test indicated that these two means were significantly different ($p < .001$). Thus restricting analysis to A quality data is omitting individuals with the lowest ambient concentrations and maybe biasing analyses toward the null hypothesis.

The distribution of ambient mean concentration of PM2.5 was tri-modal, see Figure 1 of Paper 17, which indicates a certain discreteness in the data. The discreteness may result from the limited number of airport visibility markers used as well as having airport visibility data available only at 9 airports. As a check on our analyses, 3 categories for ambient mean concentration of PM2.5 - low, medium, and high were selected to correspond to the tri-model distribution indicated in Figure 1 of Paper 17. The low category was defined as ambient mean concentration less than 20 $\mu g/m^3$. The medium category was defined to be 20-39 $\mu g/m^3$ and the high category 40 $\mu g/m^3$ or greater. Using the group of individuals in the low category as a reference group, two dummy variables were defined to indicate medium and high ambient concentration categories respectively, and the multiple logistic regression analyses for new cases of AOD, chronic bronchitis, and asthma were repeated representing mean concentration of PM2.5 by the two dummy variables and the same set of covariates as used previously.

For development of new cases of AOD, the relative risk of medium versus low ambient concentrations was 1.62 (95% C.I.: 1.05, 2.51). The relative risk for high versus low was 1.44 (95% C.I.: 0.94, 2.21). Thus there is a lack of dose response trend with a lower relative risk for high versus low than for medium versus low. For chronic bronchitis the relative risk for medium versus low was 1.53 (95% C.I.: 0.93, 2.52); the relative risk for high versus low was 1.64 (95% C.I.: 1.02, 2.63) indicating a dose response type trend. For asthma the relative risk for medium versus low was 0.97 (95% C.I.: 0.41, 2.34); the relative risk for high versus low was 1.31 (95% C.I.: 0.58, 2.93) indicating somewhat of a lack of dose response for asthma, since the relative risk for medium versus low was less than 1.

This same problem of discreteness of the data existed for the exceedance frequencies in excess of 20, 30, and 40 $\mu g/m^3$ and may account for the lack of dose response trend observed with increasing cutoffs. The distributions of exceedance frequency (see Figures 3, 4, and 5 of Paper 17) indicate that higher cutoffs than 40 $\mu g/m^3$ could have been chosen as a large percentage of the cohort had many hours in excess of 40 $\mu g/m^3$. This lack of sufficient range in the cutoffs may also account for a lack of dose response observed across cutoffs. However the discreteness of the data arising from the way airport visibility measures are measured with markers at a limited number of discrete distances would mitigate against further effort in generating additional exceedance frequencies statistics for PM2.5. In summary, because of the discrete nature of the data and the manner in which PM2.5 is indirectly estimated from visibility, one should be cautious about a quantitative interpretation of these results in terms of at what level health effects begin or in terms of quantifying relative risk.

Each of the multiple logistic regression models for development of new cases of a respiratory symptoms complex included as a covariate whether or not the subject had "possible" symptoms of the condition in 1977. This covariate was always strongly and highly statistically significantly related to development of definite symptoms between 1977 and 1987. Ambient concentrations of PM10 or other pollutants prior to 1977 may have contributed to the development of possible symptoms in 1977; hence there may be confounding between the covariate "possible symptoms in 1977" and ambient concentrations of PM10 prior to 1977. To assess this possibility, the multiple logistic regression models for development of AOD, chronic

bronchitis, and asthma were re-run with the "possible symptoms" covariate excluded. For each respiratory symptoms complex, the magnitude and level of statistical significance of the regression coefficients for mean concentration of PM2.5 increased when "possible symptoms" in 1977 was excluded as a covariate, indicating that confounding may indeed be present. The probability associated with the regression coefficient for chronic bronchitis was less than 0.05, but the probabilities associated with the other coefficients were not.

Similarly, the multiple linear regressions for change in symptoms severity score included the symptoms severity score in 1977 as a covariate, and we investigated the impact of deleting it from the models. The standardized regression coefficients relating mean PM2.5 concentration to change in AOD and chronic bronchitis symptom scores decreased, and these coefficients were no longer statistically significant. There was no change in the magnitude or significance of the standardized coefficient for asthma.

The inclusion criteria for health effects analyses required individuals to have good ambient concentration data for 80% of their months of residence 1966-1986. It was discovered in actual health effects analyses, that the time period 1966 - March, 1977, came in as the most significant time period for ambient concentrations of PM2.5; thus in retrospect it would have been necessary only to exclude individuals who did not live at least 80% of their months during this time period. If this latter exclusion criteria were applied it would have increased the numbers available for analyses for development of AOD from 1,588 to 1,894. The final model for development of AOD symptoms was rerun on this larger group. Results agreed very closely with what was done previously. For chronic bronchitis, the number of individuals would have been increased from 1,631 to 1,940. When the final model was rerun on this larger group of individuals the statistical significance of ambient mean concentration of PM2.5 increased to less than 0.05. For asthma the number of individuals was increased from 1,798 to 2,146. When the final model was rerun for asthma there was no change.

§ 10.5 Other Chronic Disease Outcomes

There were no statistically significant relative risks associated with ambient concentrations of PM2.5 for cancer incidence in males, ischemic heart disease mortality, respiratory disease mortality or all natural cause mortality in the cohort. This was true for adjusted and unadjusted mean concentration of PM2.5 and for the three cutoff levels of 20,30 and 40 $\mu g/m^3$ of PM2.5. Indeed, in many instances, the coefficients were negative in sign and in no instance was there a suggestion of increasing risk of those health outcomes with increasing ambient concentration of PM2.5 (data not shown).

However, significantly elevated relative risks of cancer incidence in females were associated with PM2.5. In Table 10.7 *Table 1 of Paper 12*, the relative risks for 20 $\mu g/m^3$ of PM2.5 associated with cancer incidence in the females are displayed along with the relative risks for the other covariates in the multivariate adjusted model (age, education and total years of smoking in the past). This table demonstrates that, for 5,000 hours per year (208 days) in

excess of 20 $\mu g/m^3$ of PM2.5 the relative risk of cancer of all sites among females is 1.74 (95% C.I.: 1.11, 2.72). Thirty percent of the person years in the study population experienced this number of hours in excess of 20 $\mu g/m^3$ of PM2.5. Additionally the covariates for age, education and total years of smoking in this table are all in the expected direction and of the expected magnitude.

Table 10.8 *Table 2 of Paper 12* presents multivariate adjusted relative risks and associated 95% confidence intervals for 20, 30 and 40 $\mu g/m^3$ of PM2.5 as well as for adjusted and unadjusted mean concentration of PM2.5 and visibility as it was related to cancer incidence in the females. Nearly all of the metrics of PM2.5 are associated with statistically significant elevations in the relative risks for cancer in females which range from 1.21 (borderline statistical significance) to 2.54 (highly significant). However, it is noteworthy that for a constant number of hours per year in excess of the three cutoff levels (20, 30, 40 $\mu g/m^3$) there does not appear to be a gradient of increasing risk of cancer among the females. For example, for a constant of 5,000 hours per year the relative risks associated with these three cutoff levels are 1.74, 1.68 and 1.62 respectively. This lack of dose response may be due to the problem of the discrete nature of the visibility data discussed previously.

These results were derived from Cox proportional hazards regression analyses in which the air pollution variable was treated as continuous. However, due to the discrete nature of the data other analyses were conducted in which the air pollution variable was categorized into two or three levels. For example, a stratified Mantel-Haenszel approach was used by creating tertiles of levels of PM2.5 corresponding to $<$2,000, 2,000-7,000 and $>$7,000 hours per year in excess of 20 $\mu g/m^3$ of PM2.5. The resulting relative risks from this analysis were 1.00, 0.83 and 1.24 respectively. When the cutpoints were changed to reflect $<$5,000 and $\geq$5,000 hours per year, however, the relative risks were 1.00 and 1.94 (95% C.I.: - 1.17, 3.21). Similar results were obtained when a Cox model was used again only with dummy variables reflecting the discrete distribution of PM2.5.

§ 10.6 Sensitivity Analyses for Other Chronic Disease Outcomes

Using an indoor infiltration factor 0.8 obtained from Winer (1989) and estimates of season of time spent indoors obtained from study participants 1977, adjusted estimates of ambient mean concentrations for study participants were formed. The results of analyses pertaining to adjusted ambient mean concentrations of PM2.5 were mentioned above, along with the results for unadjusted mean concentrations.

Another sensitivity analysis restricted study participants to those who lived at least 80% in an A quality zip code area for which assignment of estimated PM2.5 was felt to be more reliable. Results concurred with the results of the analyses for which this restriction was not made.

Table 10.1 ***Table 1 of Paper 17***
Number of Paired Data Points, Number of Study Subjects, Estimated Mean Concentration of PM2.5 1966-1986, and Standard Errors, for Airport Areas in AHSMOG Study.

Number	Airport Name	n_p †	n_s ‡	$\overline{X}$ §	Standard Error //
01	San Francisco (Alameda)#	80	58	15.37	0.43
02	San Jose#	118	192	18.61	0.45
03	Bakersfield	172	14	28.77	1.04
04	Fresno	45	28	26.38	1.23
05	Los Angeles	315	100	28.52	0.51
06	Long Beach	215	208	31.31	0.58
07	Ontario-Central	59	38	39.41	0.70
08	Ontario-East	335	779	47.64	0.75
09	Ontario-West	252	171	29.68	0.42
10	Sacramento	69	26	18.56	0.25
11	San Diego	22	253	15.68	0.19

† Number of paired PM10/TSP data points available for forming regression estimation equations.
‡ Number of study subjects living in airport area in 1987.
§ Average of estimated monthly mean PM2.5 in $\mu g/m^3$ over 252 months 1966-1986.
// Standard error of mean averaged over 252 months 1966-1986.
Data from San Francisco and San Jose were pooled for estimation of PM2.5 concentrations in the combined airport areas.

Table 10.2 ***Table 2 of Paper 17***
Multiple Logistic Regression for New Cases of Definite Symptoms of AOD in 1987, with Estimated Average Annual Mean Concentration 1966 Through March 1977 of PM2.5

(N= 1588, cases = 135)

Variable	Regression Coefficient	Increment†	Relative Risk‡	95% C.I. for Relative Risk
PM2.5 mean concentration	0.0092	45 $\mu g/m^3$	1.46	0.84, 2.46
Possible symptoms in 1977	1.2673***	(0 = no 1 = yes)	2.92	2.16, 3.85
Childhood AOD	0.7182*	(0 = no 1 = yes)	1.90	1.15, 3.02
Childhood colds	0.3463**	1 Unit	1.39	1.12, 1.71
Gender	0.3970*	(0 = no 1 = yes)	1.43	1.01, 2.00
Age	-0.0004	10 Years	1.00	0.86, 1.15
Education	-0.0503	4 Years	0.83	0.65, 1.06
Constant	-3.4144***			

† Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)

‡ Relative risk of increase in exposure of one increment, holding other variables in model constant.

* $p < .05$
** $p < .01$
*** $p < .001$

Table 10.3 ***Table 3 of Paper 17***
Multiple Logistic Regression for New Cases of Definite Symptoms of Chronic Bronchitis in 1987, with Estimated Average Annual Mean Concentration 1966 Through March 1977 of PM2.5

(N= 1631, cases = 117)

Variable	Regression Coefficient	Increment†	Relative Risk‡	95% C.I. for Relative Risk
PM2.5 mean concentration	0.0137	45 $\mu g/m^3$	1.81	0.98, 3.25
Possible symptoms in 1977	1.1922***	(0 = no 1 = Yes)	2.96	2.07, 4.16
Childhood colds	0.4495**	1 Unit	1.54	1.22, 1.93
Gender	0.3208	(0 = female 1 = male)	1.36	0.91, 2.00
Age	0.0051	10 Years	1.05	0.89, 1.23
Education	-0.0409	4 Years	0.86	0.65, 1.13
Constant	-4.4399***			

† Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)

‡ Relative risk of increase in exposure of one increment, holding other variables in model constant.

** $p < .01$

*** $p < .001$

Table 10.4 ***Table 4 of Paper 17***
Multiple Logistic Regression for New Cases of Definite Symptoms of Asthma in 1987, with Estimated Average Annual Mean Concentration 1966 Through March 1977 of PM2.5 (N= 1798, cases = 40)

Variable	Regression Coefficient	Increment†	Relative Risk‡	95% C.I. for Relative Risk
PM2.5 mean concentration	0.0078	45 $\mu g/m^3$	1.41	0.47, 4.06
Possible symptoms in 1977	4.1262***	(0 = no 1 = yes)	25.79	15.09, 34.78
Years Worked with Smoker 1973-1987	0.0373*	(0 = no 1 = yes)	1.04	1.01, 1.07
Gender	-0.2249	(0 = female 1 = male)	0.80	0.38, 1.67
Age	-0.0256	10 Years	0.78	0.59, 1.04
Education	-0.0044	4 Years	0.98	0.57, 1.69
Constant	-3.1012*			

† Increment for computations of relative risks. For childhood colds, the increment is 1 point on a 5 point scale. (1 = much less, 2 = less, 3 = same, 4 = more, 5 = much more than other children of the same age.)

‡ Relative risk of increase in exposure of one increment, holding other variables in model constant.

* $p < 0.01$

*** $p < 0.001$

Table 10.5 ***Table 5 of Paper 17***
Estimates of Relative Risk for Definite Symptoms of AOD, Chronic Bronchitis, and Asthma from Multiple Logistic Regression for Incremental Increases of Exposure in Mean Concentration and Above Various Cutoff Levels of Estimated PM2.5.

			Relative Risk Estimate		
Cutoff Level	**Increment† in Hours/ Days Per year**	**Percent Population Exposed**	**AOD**	**Chronic Bronchitis**	**Asthma**
20 $\mu g/m^3$	4000 (166.7)	69.6	1.31	1.41‡	1.08
30 $\mu g/m^3$	4000 (166.7)	40.1	1.26	1.36	1.17
40 $\mu g/m^3$	4000 (166.7)	36.3	1.26	1.41	1.26
Mean Concentration	45 $\mu g/m^3$	36.2	1.46	1.81	1.41

† Increment for computations of relative risk. Hours per year 1966 through March, 1977.
‡ Regression coefficient from which relative risks are calculated is statistically significant ($p < .05$).

Table 10.6 *Table 6 of Paper 17*
Linear Regression Models for Change in Symptoms Scores

Variable	AOD (n = 1817)		Chronic Bronchitis (n = 1826)		Asthma (n = 1798)	
	Entry Order	Standardized Reg. Coeff.†	Entry Order	Standardized Reg. Coeff.‡	Entry Order	Standardized Reg. Coeff.§
PM 2.5 Mean Concentration	7	0.051//	6	0.040//	6	0.049#
1977 Symptoms Score	1	-0.318	1	-0.507	4	-0.055
Childhood Colds	4	0.068	3	0.090		Not in
AOD Before Age 16	2	0.097		Not in	1	0.113
Years Smoked in Past	3	0.053	2	0.096		Not in
Years Worked With Smoker 73-77	6	0.063		Not in	2	0.077
Presently Live With Smoker in 1987		Not in		Not in	3	0.057
Years Dust Exposure at Work 73-77	8	0.056	5	0.046		Not in
Gender (0=female, 1=male	10	-0.027	8	-0.009	5	-0.039
Age	9	0.047	4	0.074	8	-0.031
Education (Yrs.)	5	-0.052	7	-0.040	7	-0.040
Constant Coefficient						
Achieved R^2		0.11		0.26		0.027

† All regression coefficients were statistically significant ($p < .05$) except for gender.
‡ All regression coefficients were statistically significant ($p < .05$) except for gender, education.
§ All regression coefficients were statistically significant ($p < .05$) except for gender, age and education.
// Average for years 1977-1987.
Average for years 1966-1977.

Table 10.7 ***Table 1 of Paper 12***
Cox Proportional Hazards Regression For All Malignant Neoplasms Among Females, 1977-1982, with Average Annual Hours in Concentration in Excess of 20 $\mu g/m^3$ of PM2.5 as the Air Pollution Exposure Variable.

(cases = 103)

Variable	Regression Coefficient	Increment*	Relative Risk+	95% C.I. for Relative Risk
PM2.5 (hours in excess of 20 $\mu g/m^3$)#	0.0001104	5000	1.74	1.11, 2.72"
Age	0.0024	10 y	1.02	1.01, 1.04
Education	0.0087	4 y	1.04	0.78, 1.38
Years Smoked	0.0186	10 y	1.20	0.88, 1.66

* Increment for computations of relative risk.
\+ Relative risk of increase in exposure of one increment, holding the other variables in the model constant.
\# Average annual hours in excess of 20 $\mu g/m^3$, 1966-1977.
" P = 0.0156.

Table 10.8 ***Table 2 of Paper 12***
Estimates of Cancer Incidence, In Females from Cox Proportional Hazards Regressions for Incremental Increases of Exposure above Various Cutoff Levels of PM2.5 and for Mean Concentration of PM2.5 and Visibility 1966-1977.

	Relative Risk (95% C.I.)		
	Increment	PY in Excess of Increment(%)	Incidence of all Malignant Neoplasms Females[1]
PM2.5 20$\mu g/m^3$	5000 Hrs/yr.	30	1.74(1.11,2.72)
	6000 Hrs/yr.	29	1.94(1.13,3.32)
	7000 Hrs/yr.	25	2.17(1.16,4.05)
	8000 Hrs/yr.	16	2.42(1.18,4.95)
PM2.5 30$\mu g/m^3$	3000 Hrs/yr.	35	1.36(1.05,1.77)
	4000 Hrs/yr.	27	1.51(1.07,2.15)
	5000 Hrs/yr.	20	1.68(1.08,2.60)
	6000 Hrs/yr.	19	1.86(1.10,3.15)
PM2.5 40$\mu g/m^3$	2000 Hrs/yr.	35	1.21(1.00,1.48)
	3000 Hrs/yr.	23	1.33(.99,1.79)
	4000 Hrs/yr.	21	1.47(.99,2.18)
	5000 Hrs/yr.	21	1.62(.99,2.65)
PM2.5 Mean Concentration	30 $\mu g/m^3$	41	1.59(1.03,2.46)
	40 $\mu g/m^3$	37	1.86(1.04,3.32)
	50 $\mu g/m^3$	22	2.17(1.05,4.48)
PM2.5 Adjusted Mean Concentration	20 $\mu g/m^3$	48	1.46(1.02,2.09)
	30 $\mu g/m^3$	27	1.77(1.04,3.02)
	40 $\mu g/m^3$	25	2.14(1.05,4.36)
Visibility	2 ext. Coeff[2]	51	1.59(1.04,2.45)
	3 ext. Coeff[2]	25	2.01(1.06,3.83)
	4 ext. Coeff[2]	24	2.54(1.08,5.99)

[1] Adjusted for age, education and total years of past smoking.
[2] Visibility is measured in extinction coefficients.

Chapter 11

Multipollutant Analyses

§ 11.1 Introduction

Multipollutant analyses were conducted to determine which of the ambient pollutants studied was most strongly associated with each of the disease outcomes. Strength of association was measured by level of statistical significance. Some tables which normally would have been included in this chapter are included, instead, in Chapter 12 since Chapter 12 is designed to be as much as possible a stand-alone summary chapter. Ambient pollutants are correlated with each other. Table 12.1 shows the correlations between 1977-1987 mean concentrations of ambient pollutants as estimated for study participants in the Respiratory Symptoms Cohort.

It is possible that a particular pollutant, say pollutant "A", is significantly associated with a health outcome only by virtue of the correlation between pollutant "A" and pollutant "B"; where pollutant "B" is more strongly associated with the health outcome than pollutant "A". A relationship, such as that between pollutant "A" and the health outcome, (which is really due to the association of pollutant "B" and the health outcome) will be termed a "surrogate relationship", since "A" is serving as a surrogate for "B". Each statistically significant association of a pollutant with a disease outcome was studied to determine if it might be a surrogate relationship. Although we will discuss the strength of association between health outcomes and PM10 and PM2.5, it is not possible to address the issue of surrogate relationships for these two pollutants because they were indirectly estimated from other measures - TSP in the case of PM10 and visibility in the case of PM2.5. The increased measurement error due to indirect estimation may bias the associations of these two pollutants with health outcomes.

§ 11.2 Statistical Methods

§ 11.2a Methods for Single-Pollutant Analyses

Single-pollutant analyses were conducted for each health outcome as described in Chapter 3 to determine if a pollutant had a statistically significant association with that health outcome. For development of AOD, chronic bronchitis, or asthma between 1977 and 1987, multiple logistic regression models were used to study such associations adjusting for other covariates. For change in symptoms severity between 1977 and 1987, multiple linear regressions adjusting for covariates were used. For incidence of cancer, MI, and all natural cause mortality, Cox proportional hazards regressions, adjusting for covariates were used.

The covariates used for each pollutant and health outcome are described in Chapters 4-10. A given health outcome had essentially the same set of covariates for each pollutant with minor variations in the form of the covariates for those covariates which could be averaged or

cumulated over different time periods. For example, years lived with a smoker could be the number of years between 1977 and 1987, or cumulated over all years prior to 1977. It also could be in the form or a dummy variable, indicating whether or not living with a smoker in 1977, or a dummy variable indicating whether or not living with a smoker in 1987. Averages over different time intervals of the same ambient concentration index for a pollutant competed for entry into models and averages over different time periods did enter first into different models. Gender, age, and education were forced into all models. Years of fume exposure at work was used for models relating health to gaseous pollutants. This was replaced by years dust exposure at work for models relating health effects to particulate pollutants.

§ 11.2b Methods for Multipollutant Analyses Not Involving PM2.5

Comparisons between pollutants not involving PM2.5 were performed on the entire cohort. Two different types of comparisons were used to decide which pollutant was most strongly associated with a given health outcome: (1) comparisons of levels of statistical significance of ambient concentration indices and (2) order of entry of ambient concentration indices into stepwise regressions. Since excess concentration statistics are very highly correlated with exceedance frequency statistics, only exceedance frequency statistics were studied in the multipollutant analyses.

Comparisons of the levels of statistical significance of the most significant exceedance frequency indices were made in all the multipollutant analyses. The levels of statistical significance of the mean concentrations were compared only if at least one of the mean concentrations was significantly related to the health outcome. The pollutant with the most significant of the ambient concentration indices being compared was judged to have the most significant relationship. These comparison rules may have conflicting results if both the mean concentration indices and the most significant exceedance frequency indices are being compared. Such conflicting results occurred only in the comparison between TSP and ozone. For many outcomes, only one or two pollutants were significantly associated with the outcome, and it was clear which of these pollutants had the most statistically significant relationship.

If the comparison of levels of statistical significance was judged not to be informative, the most statistically significant exceedance statistics and/or the mean concentrations of the pollutants were allowed to compete for entry into stepwise regressions of the outcome, and the pollutant entering first was judged to be the most strongly related. Gender, age, education, and the covariates that were significant in the single-pollutant analyses were forced into the model before the ambient concentration indices were allowed to compete for entry.

The discussion of each multipollutant analysis in this section specifies which type(s) of comparisons were made and which exposure indices were compared.

§ 11.2c Methods for Multipollutant Analyses Involving PM2.5

Modifications of the above methods were used for comparisons between PM2.5 and the other pollutants. These comparisons were restricted to the "airport subcohort" living in the vicinities of the ten airports at which estimated PM2.5 ambient concentrations were computed. Only the significance levels of mean concentrations of PM2.5 and other pollutants were compared for each health outcome. Comparisons involving pollutants' most significant exceedance frequency statistics were not made, because the discreteness of the PM2.5 exceedance frequency statistics' distributions suggests that the reliability of these statistics is questionable (see Chapter 10).

For each health outcome, the final single-pollutant models for the pollutants being compared were fitted to the airport subcohort with mean concentration as the ambient concentration index. Comparisons of how strongly PM2.5 and other pollutants were related to health outcomes were made by comparing the significance levels of the pollutants' mean concentration coefficients in these regressions. Details of the fitting and the criterion by which pollutants were compared will be described later in this section.

Comparisons of the order of entry into stepwise regressions were not performed. We were concerned about the possibility that increased measurement error in PM2.5 due to indirect estimation might bias the significance levels of PM2.5 coefficients and hence bias the order of entry of pollutant terms into stepwise regressions. Because of these concerns, we did not compute stepwise regressions in which PM2.5 and other pollutants were allowed to compete for entry into the same model.

Exposures to numerous pollutants were significantly associated with the respiratory endpoints -- development of and change in severity of symptoms of AOD, chronic bronchitis, and asthma. To make comparisons between pollutants for these endpoints easier, Table 11.1 displays the z-statistics of the regression coefficients of mean concentration for these endpoints. The inclusion of z-statistics for mean concentrations for more than one time period in Table 11.1 will be explained below. Only one or two pollutants were significantly associated with each of the non-respiratory outcomes, and the z-statistics for these outcomes are reported and compared in the text.

The final models for all the pollutants were fitted with mean concentration between April 1977 and March 1987, the period between the first and second questionnaires, as the exposure variable. Only models using this mean concentration could be directly compared to SO_4 models; ambient concentrations to SO_4 before 1977 could not be estimated because there was insufficient monitoring. The post-1977 period for PM2.5 and visibility is slightly different (April 1977 through December 1986), because visibility data was only available through December 1986.

For some pollutants and outcomes, the mean concentration during a period before 1977 was more statistically significant than the 1977-1987 mean in the final single-pollutant models. The final models for these pollutants and outcomes were also fitted with this more significant

mean concentration as the ambient concentration index. For most pollutants the earlier more statistically significant time period was January 1973-March 1977. This period was used as a surrogate for exposures between 1966 and 1977 because many additional monitoring stations were established in 1973. For PM2.5 and visibility, the earlier time period is January 1966-December 1977, because airport visibility data of good quality was available for January 1966-December 1986.

The criterion for comparing the strengths of association of PM2.5 and another pollutant with a health outcome compared the PM2.5 z-statistic for the most significant time period with the other pollutant's most significant z-statistic. The pollutant with the largest z-statistic was judged to be the more strongly associated.

§ 11.3 Summary of the Multipollutant Analyses

Table 12.3 summarizes the results of the multipollutant analyses. No statistically significant associations were seen between either SO_2 or NO_2 and any of the health outcomes studied in the prospective data collected since 1977; hence SO_2 and NO_2 are omitted from Tables 11.1 and 12.3. No associations were observed between visibility and health outcomes except for mean visibility and increasing severity of asthma symptoms (Paper 17) and mean visibility and incidence of all malignant neoplasms in females (Paper 12). These observed associations with visibility, however, were not as statistically significant as the associations with PM2.5 and were likely a consequence of the correlation between PM2.5 and visibility.

Table 12.3 contains a great deal of information; this paragraph explains how to read the table. Each cell in Table 12.3 indicates whether the mean concentration and exceedance frequency statistics of the pollutant of the column were statistically significantly related to the health outcome of the row. The word "None" in a cell in Table 12.3 indicates that none of the pollutant's indices were significantly related. A cutoff value without a "+" indicates that the exceedance frequency for that cutoff was statistically significantly associated with the health outcome. The "+" sign beside an exceedance frequency cutoff (e.g., 100+ in the TSP column) indicates that exceedance frequencies for that cutoff (e.g., 100 $\mu g/m^3$) and all higher cutoffs (e.g., 150, and 200 $\mu g/m^3$ for TSP) were statistically significantly associated. All of the cutoffs for each pollutant are given in Table 2.1; Table 2.1 also identifies cutoffs equal to federal and state standards. Pollutants in parentheses in Table 12.3 had a stronger association with the disease outcome than the pollutant of the column heading, which may indicate that the pollutant of the column heading has a surrogate relationship with the disease outcome.

Some cells in Table 12.3 contain the entry "Not Done." Associations with cancer outcomes with SO_4 were not studied, since SO_4 ambient concentration were calculated only for 1977 and later years, concurrently with ascertainment of cancer incidence, and it was felt that there was not sufficient lag time between exposure and incidence ascertainment. Associations of visibility and PM2.5 with respiratory cancer incidence and incidence of MI were not studied due to insufficient numbers of incident cases in the airport subcohort.

The multipollutant analyses of relationships with health outcomes summarized in Table 12.3 will be discussed in the following sections of this chapter. All of the results are based on comparisons of the levels of statistical significance obtained for each pollutant in single-pollutant analyses, unless it is specifically stated that two or more pollutants were allowed to compete for entry into the same model. When two or more pollutants were allowed to compete for entry, all of the other significant covariates were first forced into the model.

§ 11.4 Development of AOD

Development of AOD between 1977 and 1987 showed statistically significant associations with TSP and PM10. Mean concentration of TSP and exceedance frequencies for 100 $\mu g/m^3$ and higher showed statistically significant associations. Exceedance frequencies for 80 $\mu g/m^3$ and higher for PM10 also showed statistically significant associations. TSP showed stronger associations with development of AOD than did PM10, but this may have been because PM10 was indirectly estimated from TSP. Ambient mean concentration of SO_4 1977-1987, showed a statistically significant association with development of AOD, but only in the airport subcohort, see Table 11.1. Because this relationship was not statistically significant for the entire respiratory symptoms cohort, no entry is made for SO_4 and development of AOD in Table 12.3. This summarizes analyses described in Papers 8, 9, 15, and 17.

§ 11.5 Development of Chronic Bronchitis

Development of definite symptoms of chronic bronchitis between 1977 and 1987 was statistically significantly associated with TSP, PM10 and PM2.5. Mean concentration and exceedance frequencies of 100 $\mu g/m^3$ and higher of TSP showed statistically significant associations with development of chronic bronchitis, as did the exceedance frequencies for 100 $\mu g/m^3$ of PM10 and 20 $\mu g/m^3$ of PM2.5. The strengths of association between TSP, PM10 and PM2.5 can be compared for the airport subcohort in Table 11.1, but this comparison may be misleading due to PM10 and PM2.5 being indirectly estimated. From Table 11.1 we note that ambient concentrations of all these particulate pollutants for the time period before 1977 showed a stronger association with development of chronic bronchitis than did concentrations for the 1977-1987 time period; TSP showed the strongest association, followed by PM10 and PM2.5. Again, the question of surrogate relationships will not be addressed since PM2.5 and PM10 were indirectly estimated. This summarizes analyses described in Papers 8, 9, 15, and 17.

§ 11.6 Development of Asthma

Development of definite symptoms of asthma between 1977 and 1987 was statistically significantly associated with ambient concentrations of TSP, ozone, and SO_4. Exceedance frequencies of 150 $\mu g/m^3$ and higher for TSP and mean concentration of SO_4 were significantly associated with development of asthma. In addition exceedance frequencies for 10 pphm of

ozone had a positive association which was not quite statistically significant ($p = .056$). Gender specific analyses for ozone and asthma, however, indicated a highly statistically significant association between mean concentration of ozone and development of asthma in males ($p < .001$) but not in females (see Paper 13). Mean concentration of TSP was not significantly associated with development of asthma in males so the relationship between ozone and asthma in males does not appear to be a surrogate relationship due to TSP.

Because of the small number of new cases of asthma in males, complete multipollutant analyses for development of asthma were only conducted for both genders combined. Multipollutant analyses were first conducted for TSP and ozone as related to development of asthma (see Paper 8) and then for all three pollutants TSP, ozone, and SO_4, (see Paper 9). Multipollutant analyses for TSP, SO_4 and ozone were conducted two different ways, once with the covariate "possible symptoms in 1977" in the models and once with this covariate excluded.

We will first address multipollutant analyses with this covariate in the model. Mean concentrations of TSP, SO_4, and ozone were allowed to compete for entry in a stepwise multiple logistic regression after the other covariates listed in Table 4.3, including "possible symptoms in 1977", had been forced in. Ozone entered in preference to SO_4 or TSP. Once ozone was in the model, SO_4 and TSP failed to make statistically significant contributions.

Ambient concentration indices of TSP and ozone were then allowed to compete for entry in the multiple logistic regression. When mean concentrations of these two pollutants were allowed to compete for entry, ozone entered, but once ozone was in the model, TSP did not enter. The two pollutants were allowed to compete for entry again, this time using the most significant exceedance frequency statistic of each pollutant, which for TSP was exceedance frequencies above 200 $\mu g/m^3$, and for ozone was exceedance frequencies above 10 pphm. Exceedance frequencies in excess of 200 $\mu g/m^3$ of TSP entered in preference to exceedance frequencies in excess of 10 pphm of ozone. Again, once one pollutant was in the model the other failed to enter.

Other multipollutant pollutant analyses were then conducted excluding the covariate "possible symptoms in 1977." First mean concentrations of SO_4 and TSP were allowed to compete for entry in the multiple logistic regression model after the other covariates had been forced in, then mean concentrations of SO_4 and ozone. SO_4 entered the model in preference to both TSP and ozone. Once SO_4 was in the model, the other pollutants failed to make a significant additional contribution to the model. None of the exceedance frequency indices for SO_4 were significantly associated with development of asthma.

Thus, which pollutant is most related to development of new cases of asthma depends on whether or not the covariate, "possible symptoms in 1977," is included in the model and which of the indices for a pollutant is used - whether mean concentration or the most statistically significant exceedance frequency statistic. When the covariate "possible symptoms in 1977" is included in the models and mean concentrations of pollutants are allowed to compete for entry, ozone appears to have the strongest relationship. However, exceedance frequencies in excess

of 200 $\mu g/m^3$ of TSP show a stronger relationship with asthma than exceedance frequencies in excess of 10 pphm of ozone. When "possible symptoms in 1977" is not included in the model, SO_4 appears to have the strongest relationship. Thus it appears that TSP, SO_4 and ozone are all related to development of asthma.

Pairwise synergistic relationships between each of the three pollutants were also studied, (see Paper 9). The combined product variable of mean concentration of TSP with mean concentration of SO_4 was significantly related to development of asthma, however the statistical significance of this association was not as high for TSP or SO_4 mean concentration. Because of a very high correlation between the product variable and TSP, $r = 0.95$, as well as SO_4, $r = 0.85$, it was concluded that the product variable association may be a surrogate relationship. This summarizes analyses described in Papers 8, 9, 13, 15, and 17.

§ 11.7 Increasing Severity of AOD Symptoms

Increasing severity of AOD symptoms was significantly associated with TSP, SO_4, PM10, and PM2.5. Exceedance frequencies for 60 $\mu g/m^3$ and higher TSP cutoffs were associated with increasing severity of symptoms, as were the exceedance frequency for 6 $\mu g/m^3$ of SO_4, mean concentration and exceedance frequencies for 40 $\mu g/m^3$ and higher PM10 cutoffs, and mean concentration of PM2.5 and exceedance frequencies for 20 $\mu g/m^3$ and higher PM2.5 cutoffs.

Multipollutant analyses were first conducted for TSP and SO_4 on the entire respiratory symptoms cohort. Exceedance frequencies in excess of 6 $\mu g/m^3$ of SO_4 ($SO_4(6)$) were most highly correlated with exceedance frequencies of TSP above 60 $\mu g/m^3$ (TSP60) ($r = 0.78$). Therefore, a multipollutant analysis was conducted for change in AOD symptoms severity score in which the final linear regression model for $SO_4(6)$ (see Table 7.2) was used and TSP60 and $SO_4(6)$ were allowed to compete for entry after the other covariates had been forced into the model. TSP60 came into the model before $SO_4(6)$. Once TSP was in the model, SO_4 failed to make a statistically significant additional contribution. Although TSP60 came in before $SO_4(6)$, other exceedance frequency levels of TSP were more significantly related to change in AOD severity score, most notably TSP200. Thus these analyses suggest that SO_4 may be serving as a surrogate for TSP in associations with change in symptoms severity of AOD. Comparisons of the strength of associations of PM10 to the strength of associations of SO_4 were not made because PM10 was indirectly estimated from TSP. TSP was more strongly associated with increasing severity of AOD than was PM10, but this may be due to PM10 being indirectly estimated from TSP.

The strength of association of PM2.5 was then compared to the strengths of PM10, TSP, and SO_4 in the airport subcohort (see Table 11.1b). SO_4 had the highest level of statistical significance (z value) followed by TSP, PM10, and PM2.5. Thus, TSP shows a stronger association with increasing severity of AOD symptoms than does PM2.5, which is indicated by "(TSP)" in the corresponding cell of Table 12.3. Again, this conclusion should not be taken to be definitive, since PM2.5 is indirectly estimated. It is interesting to note in Table 11.1 that in

the airport subcohort SO_4 shows a stronger association with increasing severity of symptoms than does TSP. In the entire cohort, TSP is the more strongly associated of the two pollutants. For comparisons between TSP and SO_4, we would rely more heavily on the result for the entire cohort because of its larger sample size. In view of the above findings, however, one should not rule out the possibility that SO_4 has a real association with increasing severity of AOD symptoms. This summarizes analyses described in Papers 8, 9, 15, and 17.

§ 11.8 Increasing Severity of Chronic Bronchitis Symptoms

TSP and PM2.5 were significantly associated with increasing severity of chronic bronchitis symptoms. Exceedance frequencies of 150 $\mu g/m^3$ and higher of TSP were significantly associated with increasing severity of chronic bronchitis symptoms, as were mean concentration and exceedance frequency of 20 $\mu g/m^3$ for PM2.5. When analyses were restricted to the airport subcohort, PM2.5 was more significantly associated with increasing severity of chronic bronchitis symptoms than was TSP. It is interesting to note from Table 11.1 that SO_4 is slightly more significantly associated with increasing severity of chronic bronchitis symptoms than PM2.5, although SO_4 was not significantly associated with this outcome in the entire respiratory symptoms cohort. This summarizes analyses described in Papers 8, 9, 15, and 17.

§ 11.9 Increasing Severity of Asthma

Increasing severity of asthma was significantly associated with TSP, ozone, PM10, PM2.5 and visibility. Indices which were significantly associated with increasing severity of asthma symptoms were exceedance frequencies for TSP of 100 $\mu g/m^3$ and higher, mean concentration and exceedance frequencies for 10 and 12 pphm of ozone, mean concentration and exceedance frequencies of 50 $\mu g/m^3$ and higher for PM10, mean concentration and exceedance frequency of 40 $\mu g/m^3$ for PM2.5, and mean visibility. Multipollutant analyses were conducted on the entire respiratory symptoms cohort to determine which of TSP or ozone was more significantly associated with increasing severity of asthma. For increasing severity of asthma, stepwise linear regression showed that mean concentration of ozone enters in preference to mean concentration of TSP. However, in another stepwise multiple linear regression, the F to enter for exceedance frequencies in excess of 200 $\mu g/m^3$ TSP was tied with the F to enter for exceedance frequency for 10 pphm of ozone. Thus the association between ozone and the increasing severity of asthma symptoms does not appear to be due to a surrogate relationship with TSP, though one cannot rule out a real association between TSP and increasing severity of asthma.

When analyses were restricted to the airport subcohort, the level of statistical significance for PM2.5 was less than that of PM10 and TSP, any ozone and visibility. PM10 showed the highest statistical significance followed closely by TSP (see Table 11.1b). In summary then, increasing severity of asthma is most related to ozone, TSP, and PM10. These relationships do not appear to be surrogate relationships since at least one of the indices for each

of these 3 pollutants shows the strongest relationship with increasing severity of asthma in one or more analyses. This summarizes analyses described in papers 8, 9, 15, and 17.

§ 11.10 Incidence of all Malignant Neoplasms in Males

No relationship was seen between any of the air pollutants studied and incidence of all malignant neoplasms in males. An association of this outcome with SO_4 was not studied due to insufficient lag time between exposure and incidence ascertainment, as mentioned earlier. This summarizes analyses described in papers 7, 12 and 16.

§ 11.11 Incidence of all Malignant Neoplasms in Females

Incidence of all malignant neoplasms in females was significantly related to TSP, PM2.5 and visibility. Exceedance frequencies of 100 $\mu g/m^3$ and higher for TSP were significantly related, as were mean concentration and exceedance frequencies of 20 $\mu g/m^3$ and higher for PM2.5 and mean visibility. When analyses were restricted to the airport subcohort, PM2.5 showed the highest level of statistical significance. The z statistics were, for TSP, average annual hours in excess of 200 $\mu g/m^3$, $z = 2.2$; for PM2.5 average annual hours in excess of 20 $\mu g/m^3$, $z = 2.4$, for average annual visibility, $z = 2.08$. For mean concentration the z-statistics were: $z = 1.88$ for TSP, $z = 2.1$ for PM2.5. Thus PM2.5 shows the strongest association with all malignant neoplasms in females and the relationships with visibility is likely a surrogate one. A relationship with TSP cannot be ruled out since PM2.5 is not available on the entire cohort. This summarizes analyses described in papers 7, 12, and 16.

§ 11.12 Respiratory Cancer Incidence

Respiratory cancer incidence showed a positive association with the exceedance frequency of 10 pphm for ozone which was not quite statistically significant ($p = .055$). This was the only pollutant which had a positive association approaching statistical significance. There were only 17 incident cases of respiratory cancer in the entire cohort, and too few cases in the airport subcohort to permit an analysis. Analyses of associations with SO_4 were not conducted due to insufficient lag time between exposure and incidence. This summarizes analyses described in papers 7 and 16.

§ 11.13 All Natural Case Mortality

No associations were seen between all natural cause mortality and any of the ambient pollutants studied. This summarizes analyses described in papers 5, 7, 11, 12, and 16.

§ 11.14 Incidence of Myocardial Infarction (MI)

SO_4 was the only ambient pollutant studied which showed a statistically significant association with incidence of MI in the entire cohort. Exceedance frequencies for 6 $\mu g/m^3$ of SO_4 showed a statistically significant association with incidence of MI. The number of incident cases of MI were too small to warrant analyses in the airport subcohort for which measures of visibility and estimates of PM2.5 were available. This summarizes analyses described in papers 5, 7, 11, and 16.

§ 11.15 Summary

A summary of these multipollutant analyses by pollutant is given in the next chapter, as well as a discussion of the results.

Table 11.1 ***Table 8 of Paper 17***
Z-Values of Regression Coefficients of Ambient Pollutants for 1977-1987 and Most Significant Time Period† for the AHSMOG Cohort Living in the Vicinity of Nine Airports in California.

A. Development of New Cases 1977-1987 of:

Pollutant	AOD cases=135, n=1588	Chronic Bronchitis cases=117, n=1631	Asthma cases=40, n=1798
	z	z	z
PM2.5 '77-'86	1.15	1.68	0.50
PM10 '77-'87	1.24	1.26	1.50
TSP '77-'87	1.70	1.37	1.84
SO_4 '77-'87	2.09	1.35	1.53
OZ '77-'87	0.40	0.62	1.08
VIS '77-'86	0.80	0.92	1.24
PM2.5 '66-'77	1.37	1.90	0.62
PM10 '73-'77	2.09	2.08	----
TSP '73-'77	2.81	2.24	----
VIS '66-'77	----	1.53	1.34

B. Change in Symptoms Severity Scores 1977-1987 of:

Pollutant	AOD n=1817	Chronic Bronchitis n=1826	Asthma n=1798
	z	z	z
PM2.5 '77-'86	2.20	2.00	2.05
PM10 '77-'87	2.64	1.60	2.82
TSP '77-'87	2.69	1.62	2.80
SO_4 '77-'87	3.04	2.01	2.75
OZ '77-'87	1.60	0.86	2.61
VIS '77-'86	1.63	1.47	2.26
PM2.5 '66-'77	----	----	2.05
PM10 '73-'87	2.64	1.87	----
TSP '73-'77	----	1.93	----

† Only the z value for 1977-87 is given unless exposures for another time period had a higher z score in the model for this pollutant and outcome, in which case the z-value for that model is given also. The symbol "----" indicates exposures not included in this analysis because the same measure of exposure for 1977-1987 had greater statistical significance in the model for this pollutant and outcome. For SO_4, 1977-1987 was only time period available.

Chapter 12

Summary and Discussion

§ 12.1 Introduction

In recent years prospective studies have begun to study the association of long-term ambient concentrations of air pollutants and development of chronic disease. (Comstock, 1973; Rokaw, 1980; Detels, 1987; Dockery, 1989; EPA, 1984, 1986; Ferris, 1973, 1976; Jedrychowsky, 1988; Krzyzanowski, 1990; Lebowitz, 1993; Van der Landa, 1981; Carrozzi, 1993). Most of these studies have dealt with respiratory disease, though Dockery et al. (1993) studied all natural cause mortality. Few of these studies have been able to address the affects of many different pollutants on a wide range of disease outcomes.

The AHSMOG study cohort consists of 6,340 non-smoking Seventh-day Adventists (SDAs), selected in 1977, who had resided within 5 miles of their 1976 residence for the previous 10 years. The cohort has been followed since 1977 to ascertain numerous health endpoints. Incidence of all malignant neoplasms and myocardial infarctions (MI) was ascertained through 1982, development of definite symptoms of airway obstructive disease (AOD), chronic bronchitis, and asthma was ascertained through 1987, and all natural cause mortality was ascertained through 1986. Cumulative ambient concentrations of four particulate, and three gaseous, air pollutants have been estimated for study participants from 1967 to 1987 by interpolating monthly statistics from air monitoring stations statewide to zip codes of residence and work location.

Papers from this study (Abbey, 1989, 1991a,b; 1993a,b,c; 1994a,b,c; Euler, 1987, 1988; Hodgkin, 1984; Mills, 1991, 1993a,b) have reported on associations between ambient concentrations of air pollutants and development of different chronic diseases in this cohort and compared findings from this cohort with other studies. The effects of occupational exposures (Greer, 1993) and environmental tobacco smoke (Robbins, 1993) have also been addressed.

This chapter first gives an overview of the epidemiological and statistical methods and pollutant-specific analyses reported in previous chapters. The chapter then summarizes, by pollutant, the multipollutant analyses of Chapter 11. Multipollutant analyses were conducted to determine: (1) which pollutant was most strongly associated with each disease, and (2) which pollutants might be only indirectly associated with a disease because they were highly correlated with the most strongly related pollutant. We refer to an indirect association with a disease as a surrogate relationship.

To make references in the chapter text consistent, all papers are referred to by author and year. Papers from this study are not referred to by paper number, as they were in earlier chapters.

This chapter contains two exhibits which will assist the reader in locating detailed accounts of relationships between specific pollutants and health outcomes. The cross-reference table of Exhibit 12.1 enables the reader to determine which paper(s) from this study report on analyses of each relationship between a pollutant and a health outcome. Exhibit 12.2 relates the sequential paper numbers in Exhibit 12.1 to citations by author. For example, paper 8 is (Abbey 1993a).

§ 12.2 Epidemiological Methods

In April, 1977, 6,340 non-smoking, non-Hispanic white Seventh-day Adventist residents of California, who were members of the National Cancer Institute funded Adventist Health Study, were enrolled in a study to ascertain long-term chronic health effects of ambient air pollutants. To be included in the study, participants must have lived for 10 years or longer within five miles of their present residence and either (1) live in one of three air basins: San Francisco, South Coast (Los Angeles and Eastward), San Diego, or (2) have been selected by a random sample of residents from the rest of California. Subjects' ages in 1977 ranged from 27 to 95; 64% were female. More descriptive statistics of the cohort are given elsewhere (Euler, 1987; Mills, 1991; Abbey, 1993). Incidence of cancer and Myocardial Infarction was ascertained on the cohort from 1977 through 1982.

Subjects completed a standardized respiratory symptoms questionnaire (now part of the American Thoracic Society Questionnaire) in April, 1977 and, surviving subjects completed the questionnaire again in April, 1987. The 3,914 who completed both the 1977 and 1987 respiratory symptoms questionnaires are referred to as the Respiratory Symptoms Cohort. Computer algorithms were used in 1977 and again in 1987 to classify each individual as to whether or not they had definite, possible, or no symptoms of AOD, chronic bronchitis, or asthma (Hodgkin, 1984). In addition to this, computer algorithms scored the severity of symptoms for each of these respiratory complexes so that change in severity of symptoms could be measured between 1977 and 1987. Complete details of the algorithms used for scoring and classification are given in Appendix B.

§ 12.3 Methods for Estimation of Ambient Air Pollution Concentrations

Ambient air pollution concentrations for study participants since 1966 were summarized for each month by several types of monthly concentration statistics plausibly associated with long-term health effects of pollutants. The statistics were computed for each station in the statewide network of air monitoring stations for each pollutant and month for which the station had sufficient data.

Monthly statistics of the ambient concentrations for study subjects were estimated by interpolating the station statistics to the residence and work locations of subjects (Abbey, 1989; Abbey, 1991b). These residence and work locations were approximated by the centroids of their

zip codes. Both meteorological patterns and geographic barriers to airflow were accounted for in the interpolation formulas. Employed subjects were assumed to be at work locations between the hours of 8:00 AM and 5:00 PM on workdays and to be at home locations at all other times.

Subjects' long-term average ambient concentrations, as measured by each concentration statistic, were estimated by averaging that statistic's values for the zipcodes occupied by the subject over the years 1966-1986 or appropriate subperiods of those years. Averages over the years 1973-1987 were frequently used as surrogates for 1966-1987 averages because the number of monitoring stations was much larger in 1973 and afterwards. The statistical models by which associations between air pollutant concentrations and health endpoints were investigated represented subjects' ambient concentrations by these long-term averages.

The monthly statistics computed included mean concentrations of air pollutants, exceedance frequencies, and excess concentrations above a number of cutoffs. Exceedance frequencies were defined as the number of days during which particulate pollutants exceeded different cutoff levels or number of hours during which gaseous pollutants exceeded different cutoffs. Excess concentration statistics were defined as the sum of all the amounts by which concentrations exceeded a cutoff. Correlations between exceedance frequency and excess concentration statistics were close to one, hence results are summarized only for mean concentration and exceedance frequency statistics.

The cutoffs used for each pollutant were: total suspended particulates (TSP) - 60, 75, 100, 150, and 200 $\mu g/m^3$; particulates less than 10 microns in diameter (PM10) - 40, 50, 60, 80, and 100 $\mu g/m^3$; particulates less than 2.5 microns in diameter (PM2.5) - 20, 30, and 40 $\mu g/m^3$; suspended sulfates (SO_4) - 6, 9, 12, and 15 $\mu g/m^3$; Ozone - 10, 12, 15, 20, and 25 pphm; nitrogen dioxide (NO_2) - 5, 15, 20, and 25 pphm; sulfur dioxide (SO_2) - 2, 4, 5, 8, and 14 pphm. Table 2.1 gives the relationship of these cutoffs to state and federal air pollution standards.

Pollutants for which estimates were available for 1966-1987 were -- TSP, ozone, SO_2, and NO_2. As noted previously, more accurate estimates from 1973-1987 were used in many analyses. Suspended sulfates, SO_4, were available only from 1977-1987.

Since insufficient monitored PM10 data existed prior to 1985, it was indirectly estimated from TSP, using site and season specific regression equations (Abbey, 1994a). Though the indirect estimates tended to underestimate monitored values, the correlation between indirect estimates of PM10 interpolated to stations and monitored PM10 concentrations at these stations, cumulated over 1986 and 1987, was 0.86.

Though PM 2.5 was not monitored on a statewide basis, sufficient PM2.5 monitoring was performed between 1979 and 1986 to allow the formation of region and season specific regression equations relating PM2.5 to airport visibility measures at nine airports scattered throughout California. Approximately half the cohort lived close enough to the airports so that these regression equations could be used to estimate ambient concentrations of PM2.5 for 1966-

1986 (Abbey, 1994b). These subjects will be referred to as the "airport subcohort". The multiple R^2's for the site/season specific PM2.5 regression equations ranged from 0.28 to 0.83, with an average of 0.58. An average visibility measure was also calculated and related directly to health effects.

Both the visibility measures and the estimated PM2.5 concentrations which were derived from them had an inherent problem of discreteness. This was due to the way visibility is measured, using sightings of markers at a few discrete distances from an airport control tower. This problem of discreteness was obvious in the frequency distributions for PM2.5 and visibility. The problem was most severe for the exceedance frequency and excess concentration indices. The latter two indices were not used in multipollutant analyses because of this and health effects associations observed for these indices should be interpreted with extreme caution.

For each of the pollutants except NO_2, an adjustment factor for indoor infiltration of ambient concentrations was obtained from work by Winer (1989). These adjustment factors were used to adjust study participants' ambient mean concentrations for time spent indoors, using their estimates of hours spent indoors in winter and summer from the 1977 and 1987 questionnaires. Regression estimates of personal exposure to NO_2 were formed which used lifestyle and housing characteristics, indoor sources and ambient concentrations (Abbey, 1993c). Sensitivity analyses showed that relationships between health outcomes and adjusted ambient mean concentrations were similar to relationships with unadjusted ambient mean concentrations. Generally, the regression coefficients of adjusted mean concentrations were larger because adjusted concentrations have smaller ranges.

§ 12.4 Statistical Methods

The three primary health outcomes used in these analyses were: (1) development of definite symptoms of AOD between 1977 and 1987 among those who had no symptoms of AOD in 1977; (2) development of definite symptoms of chronic bronchitis by 1987 in those who had no symptoms of chronic bronchitis in 1977; and (3) development of definite symptoms of asthma in those who had no symptoms of asthma in 1977.

Separate multiple logistic regression models were used to study possible associations between each of the 3 outcomes and long-term cumulative ambient concentrations of air pollution. For each disease individuals having possible symptoms of that disease in 1977 were included in such analyses and a covariate identifying them was included in the model. "Possible symptoms in 1977" was first included as a covariate as it was hypothesized that those individuals who were most susceptible to ambient pollutants between 1977 and 1987 would be those whose lung health was already compromised. Sensitivity analyses were conducted excluding this covariate. This was done as it is possible that ambient pollutants prior to 1977 could have resulted in development of possible symptoms by 1977. If this were the case, including "possible symptoms" as a covariate could result in weakening the exposure disease relationship by including a covariate which was itself a link in the causal pathway. For SO_4, which was

monitored only between 1977 and 1987, this covariate was not included in the main analyses but a sensitivity analysis was conducted including it. The results of the sensitivity analyses, which were conducted for all pollutants, indicated concurrence of the disease pollutant associations with or without the "possible symptoms" covariate in the model.

Multiple logistic regression models for each pollutant were fitted with exposure represented by ambient mean concentration, exceedance frequencies above different cutoffs, and excess concentrations above different cutoffs. These analyses determined the cutoff levels at which statistically significant effects begin to occur. For each statistically significant exceedance frequency of a pollutant, increasing increments of hours above the cutoff frequency were substituted into the fitted multiple logistic regression model to give the associated increasing relative risks of the disease.

Plots were then made of relative risks versus cutoff level (see for e.g., Figure 6 of Chapter 3). These plots were called "relative risk plots." These plots are useful for relating epidemiological data to ambient air pollutant standards because they indicate at what cutoff relative risks begin to increase dramatically. Cutoffs were chosen to be both above and below existing state standards.

Plots were also made of exceedance frequency versus cutoff level for various fixed levels of relative risk (see e.g., Figure 7 of Chapter 3). These plots are called "relative risk contour plots". They are also useful for standards setting, because they show how many hours per year exposures can exceed cutoffs without the relative risk exceeding a specified level.

The difference of the 1977 and 1987 symptom scores of each respiratory disease measured the change in severity of the disease during this period (with a positive difference indicating increasing severity). Multiple linear regression analyses were used to study associations between these differences and long-term concentrations of ambient air pollution. The 1977 symptoms score was included as a covariate in these analyses, except for the SO_4 analyses.

For both multiple logistic and multiple linear regressions, gender, age, and education were forced into all models. Stepwise selection procedures were used to select statistically significant covariates ($p < .05$) from a large number of candidate covariates, which included - years smoked prior to 1977,[1] years lived with a smoker, years worked with a smoker, years of dust exposure at work for models relating health effects to particulate pollutants, years of fume exposure at work for models relating health effects to gaseous pollutants, frequency of childhood colds, and definite symptoms of AOD before age of 16. Unless otherwise stated, the term "statistically significant" will refer to the 2-tailed .05 level of statistical significance.

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[1] Many SDAs join the church later in life and have smoked before becoming an SDA; any individuals who reported smoking since 1977 were excluded.

For incidence of MI, cancer, and all natural cause mortality, Cox proportional hazards regression models were used. Further details of the epidemiological and statistical methods used are given by Abbey (1993a) and Mills (1991).

For each health outcome, multipollutant analyses compared different pollutants with significant associations by the level of statistical significance attained by the most statistically significant of the exceedance frequencies and mean concentration statistics. For many outcomes only one or two pollutants were significantly associated with the health outcome, and it was clear which pollutant showed the most statistically significant relationship. For other pollutants stepwise regression procedures were used to allow mean concentrations of the different pollutants to compete for entry in the model, if the mean concentration of one of the pollutants was significantly associated with the health outcome. If this was not the case, the most statistically significant of each pollutant's exceedance frequency statistics were allowed to compete for entry in the model. In both situations gender, age, and education, and the covariates found to be significant from the single pollutant analyses were first forced into the model; then the two pollutants were allowed to compete for entry. Comparisons between TSP, ozone, SO_4, and PM10 were made on the entire cohort. Comparisons between each of these pollutants and PM2.5 were restricted to the subcohort living in the vicinity of airports for which PM2.5 estimates were available.

§ 12.5 Results

Table 12.1 gives the correlations between the 1977-1987 estimated ambient mean concentrations of pollutants to which subjects in the Respiratory Symptoms Cohort were exposed. Table 12.2 gives the relative risks of development of respiratory diseases and of cancer for selected increments of ambient concentrations of TSP, PM10, PM2.5, SO_4, and ozone; confidence intervals for these relative risks are given. Increments in the exceedance frequencies and mean concentrations were chosen to be within the ranges experienced by the cohort. For TSP, PM10, SO_4, and ozone, the increment was expressed in terms of the most statistically significant of the ambient concentration indices, either mean concentration or the exceedance frequency above a cutoff. For PM2.5 the increment was expressed in terms of mean concentration because PM2.5 exceedance frequencies were judged to be unreliable. Some cells in Table 12.2 contain the entry "not done." Possible associations between SO_4 and cancer incidence were not analyzed since SO_4 ambient concentration statistics were available only since 1977 and it was felt that there was not sufficient lag time between these exposures and possible cancer incidence. Statistical analyses of associations of PM2.5 and visibility with respiratory cancer incidence and incidence of MI were not conducted because there were an insufficient number of subjects in the airport subcohort.

For the prospective data collected since 1977, no statistically significant associations were seen between any of the health outcomes studied and SO_2 or NO_2 (Abbey, 1991a; 1993a,c; Mills, 1993a). This result remained true when ambient concentrations of SO_2 and NO_2 were adjusted to reflect time spent indoors and when NO_2 exposures were modeled by the regression

estimates of personal exposure. No associations were observed between long term ambient concentrations and any of the ambient pollutants studied and incidence of all malignant neoplasms in males, or all natural cause mortality (Abbey, 1991a; Mills, 1991; Abbey, 1993c; Mills, 1993a,b, and 1994). No associations were observed between visibility and health outcomes except for associations between mean visibility and increasing severity of asthma symptoms (Abbey, 1994b) and mean visibility and incidence of all malignant neoplasms in females (Mills, 1993b). These observed associations with visibility, however, were not as statistically significant as the corresponding associations with PM2.5, and were likely the result of the correlation between PM2.5 and visibility.

Table 12.3 summarizes the results of the multipollutant analyses and gives the cutoffs for which exceedance frequencies show statistical significance. In Table 12.3 symbols of the form "100+" indicate that significant associations with the health outcome were observed for exceedance frequencies for 100 and higher cutoffs. Symbols of the form "100" indicate that exceedance frequencies for the single cutoff 100, have statistically significant associations. Pollutants in parentheses in a cell of Table 12.3 indicate that the observed association with a health outcome could be due instead to an association between the pollutant in parentheses and the health outcome, since the pollutant in parentheses showed greater statistical significance.

§ 12.5a TSP

Ambient concentrations of TSP in excess of 100 $\mu g/m^3$ were significantly associated with many of the health outcomes. TSP showed the most statistically significant associations of any of the pollutants with development of AOD and chronic bronchitis, and also with increasing severity of symptoms for AOD and chronic bronchitis. From Table 12.3 it can be seen that ambient concentrations of TSP in excess of 60 $\mu g/m^3$ were associated with increasing severity of AOD symptoms. For asthma, TSP, ozone, and SO_4, were close competitors (see ozone and SO_4 sections below). TSP was statistically significantly associated with incidence of all malignant neoplasms in females, but not in males. When analyses were restricted to the airport sub-cohort for which estimates of PM2.5 were available, TSP remained statistically significantly associated with incidence of all malignant neoplasms in females but was not as statistically significant as PM2.5. Relative risk plots and relative risk contour plots for TSP and development of AOD are given in Figures 1 and 2 of Abbey, 1993a. These results summarize information contained in Abbey, 1991a; Mills, 1991; Abbey 1993a; Mills 1993b; Abbey, 1994b.

§ 12.5b Ozone

Ozone was highly significantly associated with development of asthma in males but not females. This relationship does not appear to be a surrogate relationship. The relative risk for a 1 pphm increase in mean concentration of ozone was 3.12, (95% C.I.: 1.61, 5.85), (Greer, 1993). In non-gender specific analyses exceedance frequencies above 10 pphm of ozone showed a positive association with development of asthma which was not quite statistically significant

(p = .056). Ozone was more strongly associated with development of asthma than TSP when mean concentrations of the two pollutants were allowed to compete for entry in the models, but was less strongly related when the most significant exceedance frequency statistic of each pollutant was used, i.e., TSP in excess of 200 $\mu g/m^3$ showed a higher statistical significance than ozone in excess of 10 pphm.

Mean concentration of ozone and exceedance frequencies for the two lowest cutoffs, 10 pphm and 12 pphm, showed statistical significance when associated with increasing severity of asthma. For increasing severity of asthma, stepwise linear regression showed that mean concentration of ozone enters in preference to mean concentration of TSP. However, in another stepwise multiple linear regression, the F to enter for exceedance frequencies in excess of 200 $\mu g/m^3$ TSP was tied with the F to enter for exceedance frequencies in excess of 10 pphm of ozone. Ozone showed a strong positive association with respiratory cancer incidence. (See Table 12.2.) Due to the small number of incident cases, only 17, this association was not statistically significant (p = .055). This summarizes results contained in Mills, 1991; Abbey, 1993a; and Abbey, 1994b.

§ 12.5c SO_4

SO_4 was statistically significantly associated with development of asthma and was more significantly associated than TSP or ozone when the covariate, "possible symptoms in 1977" was not included in the model.

Analyses based on the entire respiratory symptoms cohort indicated that the relationship between SO_4 and increasing severity of AOD symptoms may instead be due to TSP and the correlation between SO_4 and TSP. When analyses were restricted to the airport sub-cohort, however, SO_4 was more significantly associated with increasing severity of AOD symptoms than any of the other pollutants, including TSP.

Exceedance frequencies above 6 $\mu g/m^3$ were significantly associated with incidence of MI (Abbey, 1993b). None of the other indices of SO_4 were significantly associated with MI. SO_4 was the only pollutant studied which showed an association with incidence of MI. However, the lack of association between incidence of MI and exceedance frequencies for other cutoffs higher than 6 $\mu g/m^3$ makes one wonder if this result just occurred by chance. This is a summary of results contained in Abbey 1993a; Mills 1993a; and Abbey 1994b.

§ 12.5d PM10

Because indirect estimation of PM10 from TSP may have biased PM10 coefficients, direct comparisons of the strengths of association on PM10 and other pollutants cannot be considered conclusive. Exceedance frequencies for PM10 cutoffs of 40 $\mu g/m^3$ and higher had significant associations with increasing severity of symptoms of AOD, and exceedance

frequencies for cutoffs of 80 $\mu g/m^3$ and higher had significant associations with development of AOD symptoms. The strength of these associations with AOD outcomes was exceeded only by the strength of their associations with TSP. If PM10 had not been indirectly estimated from TSP, it might have shown the strongest relationships. The same is true of the association between PM10 exceedance frequencies for the 100 $\mu g/m^3$ cutoff and development of chronic bronchitis. However, PM10 is not significantly associated with increasing severity of symptoms of chronic bronchitis. PM10 showed a statistically significant association with increasing severity of asthma symptoms, as did ozone. Multipollutant analyses comparing PM10 and ozone were conducted but the results of these multipollutant analyses should be viewed with caution because of possible biases in the PM10 relationships. PM10 had a stronger association than ozone when exceedance frequency indices were used. On the other hand ozone showed a stronger association with this outcome than either PM10 or TSP when the mean concentration index was used. This summarizes results reported in Abbey (1994a) and Mills (1994). A relative risk plot and relative risk contour plot relating risks of developing new cases of AOD to PM10 exceedance frequencies are given in Abbey (1994a).

§ 12.5e PM2.5

Because PM2.5 was indirectly estimated from visibility, comparisons of strengths of association with other pollutants cannot be regarded as conclusive. Exceedance frequencies for the cutoff of 20 $\mu g/m^3$ of PM2.5 were statistically significantly associated with development of chronic bronchitis. The strength of the association of mean concentration of PM2.5 with development of chronic bronchitis was not as high as the strengths of TSP and PM10 when analyses were restricted to the airport subcohort for which PM2.5 estimates were available.

PM2.5 was significantly associated with increasing severity of AOD symptoms but was less significantly associated than TSP or SO_4 when analyses were restricted to the airport subcohort. SO_4, in fact, showed the highest level of significance. PM2.5 was significantly associated with increasing severity of chronic bronchitis. However, the level of statistical significance, was not as high as the level of significance of TSP for the airport subcohort. PM2.5 was significantly related to increasing severity of asthma symptoms. However, PM10 and ozone both showed stronger associations with this health outcome when analyses were restricted to the airport subcohort.

PM2.5 was significantly associated with incidence of all malignant neoplasms in females, and its level of statistical significance was higher than that of TSP when analyses were restricted to the airport subcohort. This is a summary of results contained in Mills, 1993b and Abbey, 1994b.

§ 12.6 Discussion and Conclusions

The limitations of this study have been thoroughly discussed in previous papers (Mills, 1991; Abbey, 1993a,b,c; Greer, 1993). Space does not permit reiteration of these limitations. The effects of TSP, PM10, and PM2.5 cannot be truly separated in this study due to the fact that the ambient concentrations of PM10 and PM2.5 were indirectly estimated whereas those for TSP were monitored, and also because of the high correlations between them (see Table 12.1). The increased measurement error for PM10 and PM2.5 due to indirect estimation could bias observed associations, thus making it difficult to make valid comparisons with other pollutants. Because of the large number of associations studied, some of our statistically significant associations could have occurred by chance.

Estimated ambient concentrations were needed for study participants for the period January 1966-March 1987. This overall time period was divided into three different sub-time periods before being used in analyses. The three sub-time periods for all pollutants except PM2.5 and SO_4, were: January 1973 through March 1977, April 1977-March 1987, and January 1973-March 1987. The period January 1973-March 1977 was used as a surrogate for January 1966-March 1977 for all pollutants except for PM2.5 and SO_4 because there were many more monitoring stations in 1973 and later years. Inadequate data were available for SO_4 prior to April 1977, so only one time period, April 1977-March 1987, was used. PM2.5 was estimated from airport visibilities for the years 1966-1986. Hence the three time periods for PM2.5 were: January 1966-March 1977, April 1977-December 1986, and January 1966-December 1986.

The alternative time periods were allowed so that determination could be made of whether historical and/or concomitant ambient concentrations of air pollutants were more strongly associated with development of or increasing severity of disease between April 1977 and April 1987. The stepwise selection procedures used in forming the regression models were allowed to select the most statistically significant time period. The papers from this study state which time period for each pollutant was most significantly related to each health outcome. Sensitivity analyses showed that results using averages for different time periods agreed closely.

Cox proportional hazards regression models, were used to analyze incidence of cancer and MI and mortality, events whose date was known. For Cox models, ambient concentrations of air pollutants were represented by either the average from January 1973 through date of event or risk set (time-dependent models) or the average from January 1973 through March 1977, (fixed-time models). Sensitivity analyses found that the results for the time-dependent and fixed-time models were very similar.

The respiratory symptoms complex of definite symptoms of chronic bronchitis included having definite symptoms of chronic productive cough (with sputum) and/or having definite symptoms of "cough only". See Appendix B, Exhibit 1; also Appendix A, Exhibit 1. It is believed by some that chronic productive cough (with sputum production) is less reversible than "cough only" (without sputum). Development of definite symptoms of overall chronic bronchitis

was statistically significantly associated with elevated ambient concentrations of TSP, PM10, and PM2.5. In order to determine whether this relationship was primarily due to chronic productive cough v.s. "cough only," separate analyses were conducted for each symptoms complex. The multiple logistic regressions for development of definite symptoms of chronic bronchitis as associated with exceedance frequencies for 200 $\mu g/m^3$ TSP, 100 $\mu g/m^3$ PM10, and 20 $\mu g/m^3$ PM2.5 were repeated for the subjects who did not have definite symptoms of chronic bronchitis in 1977; chronic productive cough is thought to be less reversible than "cough only." Hence separate multiple logistic regressions were conducted for development of definite symptoms of chronic productive cough and for "cough only." These analyses showed that the level of statistical significance remained the same or increased for development of definite symptoms of chronic productive cough while that for development of definite symptoms of "cough only" decreased to a little below the (.05) level for statistical significance. For chronic productive cough the regression coefficient increased and for "cough only" the regression coefficient decreased as compared to the respective regression coefficients for development of overall symptoms of chronic bronchitis. This was true for each of TSP, PM10, and PM2.5. Thus particulate air pollution is more strongly related to the less reversible form of chronic bronchitis - chronic productive cough.

No associations were observed between SO_2 and any of the health outcomes from the prospective data. An older phase of the study had shown associations between SO_2 and prevalence of definite AOD symptoms in 1977 (Euler, 1987), but multipollutant analyses indicated that the relationship may have been due to TSP (Euler, 1988). The lack of association between SO_2 and any of the disease outcomes studied in the prospective data collected since 1977 may be due to lower levels of SO_2 experienced by our cohort, compared to the levels in other studies where health effects have been observed (Mills, 1991; Abbey, 1993a). The lack of association between NO_2 and health effects seen in adults in this study does not negate associations seen in children (Abbey, 1993c; Shy, 1970; Dawson, 1979; Love, 1982; Neas, 1991).

Our finding of no association between all natural cause mortality and long term concentrations for any of the ambient pollutants studied is inconsistent with an association seen between mortality and particulates in the Six Cities Study by Dockery (1993). Survival curves for their cohort indicated the greatest differences between cities in years 8-16 of follow-up. We only had 10 years of mortality follow-up available for present analyses on our cohort, which may explain the discrepancy.

We observed that an elevated risk of all malignant neoplasms in females but not in males was associated with TSP and PM2.5 ambient concentrations. A similar result has been observed in an epidemiological study in Israel (Biger, personal communication, 1991). Gender differences have been observed in at least one animal study. Experiments in rats have shown that particulate matter in diesel exhaust fumes have a greater impact on lung tumor formation in females than males, especially at the highest concentration levels (Mauderly, 1987). Fine particulates often contain the most toxic compounds (e.g., trace metals, acid sulfates, organics, etc.) (Özkaynak,

1987). Females have been shown to have a greater deposition fraction than males of fine particles in the lungs (Kim, 1994).

Only 17 incident cases of respiratory cancer were observed in our cohort, hence results pertaining to this outcome should be viewed as very tentative. The increased risk of respiratory cancer associated with elevated ozone in our cohort is consistent with some animal studies. Dillon (1992) showed that ozone was mutagenic in Salmonella. Ozone has been shown to be carcinogenic in mice though not in rats. (Hassett, 1985; Last, 1987; National Toxicology Program Technical Report, 1993). Our findings of elevated risks of asthma and respiratory cancer associated with ozone are consistent with a significantly increased standardized incidence ratio of lung cancer observed in asthmatics in Finland (Vesterinen, 1993), and a very slightly elevated but not statistically significant standardized morbidity ratio found for respiratory tract cancer in asthmatics in Sweden (Källén, 1993).

Ozone was significantly associated with development of asthma in males but not in females. T-test between males and females in our cohort showed that males were outdoors significantly more than females during the high ozone season of June through September (Greer, 1993). Ozone is highly volatile and not stable in the indoor environment, which may explain the gender discrepancy with respect to associations of ozone ambient concentrations and development of asthma.

We found ozone to be associated with asthma and asthmatic symptoms but not chronic bronchitis. This pattern of relationships has been observed in other studies (von Mutius et al., 1992; Viegi et al., 1991; Krzyzanowski et al, 1990; Lippmann, 1989). Chronic bronchitis and chronic obstructive pulmonary disease (COPD) appear to be associated much more with reducing type (PM-SO_x) atmospheres (Sunyer et al., 1993; Lebowitz, 1983; Ware, 1980; ATS, 1978; Colley & Holland, 1967). Our findings that TSP and PM10 are more strongly associated with development of and an increasing severity of symptoms of overall AOD and chronic bronchitis than other pollutants are consistent with these findings. However, in our study SO_4 was strongly associated with development of asthma as well as increasing severity of AOD.

Lung function parameters such as post bronchodilator response as well as lability indices from home peak flow diary data have recently been collected on 1,500 members of our cohort. An additional 10 years of cancer incidence data is being collected on the entire cohort as well as an additional six years of mortality data. Ambient air pollution indices are being updated on the cohort through 1993. These updated indices will include monitored PM10, available on a statewide basis since 1987. New indices for ozone are being computed which include 8 hour averages and exceedance frequencies and excess concentrations for two new lower cutoffs, 6 and 8 pphm. Analyses of these new data may provide answers to some of the questions raised from current findings.

Chapter 12

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Table 12.1 Pairwise Correlations of Estimated Mean 1977-1987 Concentrations of Ambient Pollutants for Members of the AHSMOG Respiratory Symptoms Cohort (n = 3914)[a]

	TSP	PM10[b]	PM2.5[c]	SO_4	OZ	SO_2	NO_2
TSP	1	.95	.86	.69	.72	.61	.46
PM10[b]	. . .	1	.89	.72	.76	.64	.52
PM2.5[c]	. . .	. . .	1	.30	.62	.47	.25
SO_4	. . .	. . .	. . .	1	.57	.60	.63
OZ	. . .	. . .	. . .	. . .	1	.38	.36
SO_2	. . .	. . .	. . .	. . .	. .	1	.85
NO_2	. . .	. . .	. . .	. . .	. . .	. . .	1

[a] Correlations between PM2.5 and other ambient concentrations are computed only for 1977-1986 for individuals living in the vicinity of nine California airports, n = 1868. Correlations of other pollutants are computed for the entire cohort, n = 3914, April 1977 - April, 1987.

[b] PM10 was indirectly estimated from TSP using site/seasonal regression equations.

[c] PM2.5 was indirectly estimated from airport visibility data.

Table 12.2 Relative Risks Estimated from Multivariate Models and 95% Confidence Intervals for Selected Increments of Particulate Pollutants and Ozone

	POLLUTANT/INCREMENT						
DISEASE	n[a]	TSP 42 days/yr above 200 $\mu g/m^3$	PM10 42 days/yr above 100 $\mu g/m^3$	SO_4 Av. Annual increase of 7 $\mu g/m^3$	Ozone 500 hr/yr above 10 pphm	PM2.5 Average annual increase of 45 $\mu g/m^3$	n[b]
DEVELOPMENT OF: AOD[c]	272	1.36 (1.11, 1.66)	1.17 (1.02, 1.33)	1.43 (0.88, 2.26)	1.04 (0.86, 1.25)	1.46 (0.84, 2.46)	135
Chronic Bronchitis[d]	234	1.33 (1.07, 1.65)	1.17 (1.01, 1.35)	0.96 (0.58, 1.55)	1.02 (0.83, 1.25)	1.81 (0.98, 3.25)	117
Asthma[e]	80	1.74 (1.11, 2.71)	1.30 (0.97, 1.73)	2.85 (1.03, 7.40)	1.35 (0.93, 1.96)	1.41 (0.47, 4.06)	40
INCIDENCE OF ALL MALIGNANT NEOPLASMS Females[f]	175	1.37 (1.05, 1.80)	1.15 (0.97, 1.38)	Not Done	1.03 (0.81, 1.32)	2.01 (1.05, 3.86)	103
RESPIRATORY CANCER INCIDENCE [f]	17	1.72 (0.81, 3.65)	1.46 (0.88, 2.40)	Not Done	2.25 (0.96, 5.31)	Not done	

(a) n = number of new cases for entire cohort for whom estimated TSP, PM10, SO_4, and Ozone were available.

(b) n = number of new cases for subcohort for whom estimated PM2.5 data was available.

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

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

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

(f) Variables included as covariates in the Cox model for cancer (besides age) are total years of past smoking and education attainment.

Table 12.3 **Statistically Significant ($p < .05$) Associations of Ambient Pollutants, as Measured by Mean Concentration and Exceedance Frequency Statistics, with Disease Outcomes for the AHSMOG Study (Association with health outcome may be due to correlation with other pollutant, if it is in parenthesis, in cell)**

DISEASE		New Cases 1977-1987	TSP	PM10	PM2.5	SO_4	Ozone
DEVELOPMENT OF:	AOD	272	μ[a], 100+[b]	80+ (TSP)	None[c]	None	None
	Chronic Bronchitis	234	μ, 100+	100 (TSP)	20 (TSP)	None	None
	Asthma	80	150+	None	None	μ	[d]
INCREASING SYMPTOMS SEVERITY OF:	AOD		μ, 60+	μ, 40+ (TSP)	μ, 20+ (TSP)	6 (TSP)	None
	Chronic Bronchitis		150+ (PM2.5)	None	μ, 20	None	None
	Asthma		100+	μ, 50+	μ, 40 (TSP)	None	μ, 10, 12
INCIDENCE OF ALL MALIGNANT NEOPLASMS	Males	115	None	None	None	Not Done [e]	None
	Females	175	100+	None	μ, 20+	Not Done	None
RESPIRATORY CANCER INCIDENCE		17	None	None	Not Done	Not Done	10[f]

(a) μ = ambient mean concentration

(b) 100+, etc. exceedance frequencies of 100 and higher are statistically significant, $p < .05$. Units are in $\mu g/m^3$ for particulate pollutants - TSP, SO_4, PM10, PM2.5; for ozone units are pphm. The symbol 100 without the "+" would indicate that only exceedance frequencies for the cutoff of 100 were statistically significant.

(c) None = No statistically significant association with mean concentration or any exceedance frequency statistic.

(d) For ozone and asthma a positive association ($p = .056$) was noted for exceedance frequencies above 10 pphm and a strong statistically significant association between mean concentration and development of asthma in males but not females.

(e) Not Done = No statistical test of association made due to small number of incident cases; or in case of SO_4 insufficient lag time between exposure and incidence ascertainment.

(f) A positive association was observed between exceedance frequencies above 10 pphm ozone and incidence of respiratory cancer which was of borderline statistical significance ($p = .055$).

EXHIBIT 12.1

Cross Reference Table for AHSMOG Papers Which Address Associations Between Specific Air Pollutants and Diseases

Disease Outcome		TSP	Ozone	SO_2	NO_2	SO_4	PM10	PM2.5	Visibility
DEVELOPMENT OF:	AOD	5,8	5,8	8	10	9	15	17	17
	Chronic Bronchitis	5,8	5,8	8	10	9	15	17	17
	Asthma	5,8	5,8,13	8	10	9	15	17	17
INCREASING SEVERITY OF SYMPTOMS OF:	AOD	8	8	8	10	9	15	17	17
	Chronic Bronchitis	8	8	8	10	9	15	17	17
	Asthma	8	8	8	10	9	15	17	17
INCIDENCE OF ALL MALIGNANT NEOPLASMS IN:	Males	5,7	5,7	11	10	Not Done(1)	16	12	(2)
	Females	5,7	5,7	11	10	Not Done(1)	16	12	(2)
RESPIRATORY CANCER INCIDENCE		5,7	5,7	11	10	Not Done(1)	16	Not Done(1)	Not Done(1)
ALL NATURAL CAUSE MORTALITY		5,7	5,7	11	10	11	16	12	(2)
INCIDENCE OF M.I.		5,7	5,7	11	10	11	16	Not Done(1)	Not Done(1)

(1) Not Done = No statistical test of association made due to small number of incident cases; or in case of SO_4 insufficient lag time between exposure and incidence ascertainment.

(2) Not in an AHSMOG paper.

EXHIBIT 12.2

PUBLISHED PAPERS FROM AHSMOG STUDY

Paper #	Author & Year
1.	Hodgkin, 1984
2.	Euler, 1987
3.	Euler, 1988
4.	Abbey, 1989
5.	Abbey, 1991a
6.	Abbey, 1991b
7.	Mills, 1991
8.	Abbey, 1993a
9.	Abbey, 1993b
10.	Abbey, 1993c
11.	Mills, 1993a. Submitted for publication.
12.	Mills, 1993b. Submitted for publication.
13.	Greer, 1993
14.	Robbins, 1993
15.	Abbey, 1994a. In press
16.	Mills, 1994. To be submitted for publication.
17.	Abbey, 1994b. Submitted for publication.

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Abbey DE, Mills, PK, Petersen F, Beeson WL. (1991a) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-day Adventists. Environ Hlth Persp 1991; 94:43-50. *AHSMOG Paper 5*

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Abbey DE, Petersen FF, Mills PK, Kittle L. (1993b) Chronic respiratory disease associated with long term ambient concentrations of sulfates and other air pollutants. J of Exp Anal and Environ Epidemiol. 1993; 3(S1):99-115, *AHSMOG Paper 9*

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