HEI HEALTH EFFECTS INSTITUTE

Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure

Part I: Variability of Pulmonary Function Measures
Ira B. Tager, Nino Künzli, Long Ngo, and John Balmes

Part II: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)
Ira B. Tager, Nino Künzli, Frederick Lurmann, Long Ngo, Mark Segal, and John Balmes

Part III: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)
Patrick L. Kinney, Maneesha Aggarwal, Sergey V. Nikiforov, and Arthur Nadas

Includes the Commentary of the Institute's Health Review Committee

Research Report Number 81
March 1998

HEI HEALTH EFFECTS INSTITUTE

The Health Effects Institute, established in 1980, is an independent and unbiased source of information on the health effects of motor vehicle emissions. HEI studies all major pollutants, including regulated pollutants (such as carbon monoxide, ozone, nitrogen dioxide, and particulate matter), and unregulated pollutants (such as diesel engine exhaust, methanol, and aldehydes). To date, HEI has supported more than 170 projects at institutions in North America and Europe.

Typically, HEI receives half its funds from the U.S. Environmental Protection Agency and half from 28 manufacturers and marketers of motor vehicles and engines in the United States. Occasionally, funds from other public or private organizations either support special projects or provide resources for a portion of an HEI study. Regardless of funding sources, HEI exercises complete autonomy in setting its research priorities and in reaching its conclusions. An independent Board of Directors governs HEI. The Institute's Research and Review Committees serve complementary scientific purposes and draw distinguished scientists as members. The results of HEI-funded studies are made available as Research Reports, which contain both the Investigators' Report and the Review Committee's evaluation of the work's scientific quality and regulatory relevance.

RESULTS AND IMPLICATIONS

The studies of Tager and Kinney are important efforts to develop retrospective methods for estimating an individual's lifetime exposure to ozone. Of the methods Kinney tested on the nationwide data set, a statistical regression technique that incorporated data from the three nearest ozone monitoring sites was the most accurate and straightforward. The largest differences between predicted ozone estimates and actual readings were found predominantly in California, mostly around Los Angeles, and in the New York/New Jersey/Connecticut metropolitan area. This finding suggests that it may be difficult to make exposure estimates in locations where ozone levels are high and variable. Using this method, Kinney found that distance from the nearest monitoring site (up to 30 miles) did not affect the accuracy of the estimate. This is a reassuring finding, implying that accurate estimates of ozone can be made even in rural areas where ozone monitors are far apart. However, when Kinney applied a different statistical method (known as "kriging" and based on distance) to a subset of his data, he found that the exposure estimates improved. This implies that more work is needed to determine the impact of distance from a monitoring site on ozone exposure estimates.

Tager combined questionnaire information about residential history and activity patterns with long-term data from California ozone monitoring sites. The precision of responses from subjects on retest after a five- to seven-day interval was high. However, subjects' responses to Kinney's questionnaire about residence and activity patterns were in only moderate agreement after a one-month interval. Neither investigator attempted to confirm this information with an independent source, such as the subjects' parents. Not unexpectedly, Tager found that subjects who had resided for a long time in the Los Angeles Basin had higher estimated lifetime ozone exposures than subjects who had lived in the San Francisco Bay Area.

Tager also found in a laboratory setting that two measures of airflow through small airways ($FEF_{75\%}$ and $FEF_{25\%-75\%}$) were reproducible both from person to person and from test to test, whereas one other measure of small airway function, ΔN_2, was not. This finding confirms results from previous studies, and suggests that $FEF_{75\%}$ and $FEF_{25\%-75\%}$ may be useful measures of small airway function in future large-scale epidemiologic studies of air pollution health effects.

In a preliminary study, Tager found that the subjects who had the highest estimates of cumulative ozone exposure (those who had lived in the Los Angeles Basin) had lower $FEF_{75\%}$ and $FEF_{25\%-75\%}$ values than those who had the lowest estimates of cumulative exposure (residents of the San Francisco Bay Area). This is a provocative and potentially important finding because it suggests that subjects who have spent a long time in an environment containing high levels of ozone (and other air pollutants) may have decreased small airway function (compared with those living in a low-pollutant environment). However, because other study factors may influence these observations (such as differences between regions or among the ethnic backgrounds of subjects in different regions, and lack of overlapping ozone levels between the regions), these results should be interpreted cautiously. Studying appropriately matched subjects who have been exposed to a range of ozone levels is needed to substantiate the findings.

Tager and Kinney have taken important steps in developing approaches for retrospective estimation of past exposure to ozone. Both investigators used fixed-site ambient monitoring data accumulated over many years and devised statistical models to estimate ozone concentrations at locations distant from the monitoring sites. Their approaches are based on a number of reasonable assumptions about what influences an individual's received dose. The investigators are now ready to test and, to the extent possible, validate their methods. If such studies are successful, the investigators' methods should advance air pollution epidemiology.

Library of Congress Catalog Number for the HEI Research Report Series: WA 754 R432.
The paper in this publication meets the minimum standard requirements of the ANSI Standard Z39.48-1984 (Permanence of Paper) effective with Report Number 21, December 1988, and with Report Numbers 25, 26, 32, 51, and 65 Parts IV, VIII, and IX excepted. These excepted Reports are printed on acid-free coated paper.

HEI Statement

Synopsis of Research Report Number 81

Long-Term Exposure to Ozone: Development of Methods to Estimate Past Exposures and Health Outcomes

BACKGROUND

Short-term exposure to ozone, a ubiquitous air pollutant, is known to have adverse effects on the respiratory system. These effects, which include cough, shortness of breath, an inflammatory response in the airways, and transient changes in results on some tests of lung function, depend on the duration and intensity of exposure, as well as individual susceptibility. Although these effects appear to be reversible, there is concern that the inflammation associated with prolonged or repeated exposure may lead to permanent changes that affect the small airways. However, the effects of long-term exposure to ozone in humans are difficult to study. One major problem is estimating the concentrations of ozone that individuals have been exposed to over their lifetimes; a second issue is the variability in tests capable of measuring physiologic changes in the small airways. Thus, developing accurate methods for estimating past exposure to ozone and developing precise (that is, reliable or reproducible) tests of small airway function are critical for future studies of long-term human ozone exposure. This report describes the results of two feasibility studies that were designed to address these needs.

STUDY DESIGNS

The studies described in this report were conducted by two independent investigator groups: Dr. Ira Tager and colleagues at the University of California at Berkeley (UCB), and Dr. Patrick Kinney and colleagues at the School of Public Health, Columbia University. The objective of both groups was to develop new methods for estimating an individual's past exposure to ozone. To estimate personal exposure to ozone, both groups of investigators combined historical data from a network of ozone monitoring sites (nationwide in Kinney's study, and California-based in Tager's) with data from questionnaires that obtained information about residence history, time spent outdoors, and level of activity while outdoors. To determine the precision of the residence and activity information, both investigators administered the questionnaire a second time to their study subjects.

Tager and coworkers studied UCB students who were lifetime residents of areas of California with either high or low levels of air pollution (the Los Angeles Basin or San Francisco Bay Area, respectively). In addition to estimating personal exposure to ozone, they also determined which tests of lung function, particularly small airway function, would be the most precise to use in a future, larger epidemiologic study. As part of his study, Tager then measured lung function in subjects whose long-term exposure to ozone he had previously estimated. Kinney studied Yale University students who had lived in different regions of the United States. He focused on evaluating the accuracy of different statistical methods for estimating previous ozone exposure, and in particular, on determining how many ozone monitoring sites were needed to provide data to make accurate estimates.

This Statement, prepared by the Health Effects Institute and approved by its Board of Directors, is a summary of three research projects sponsored by HEI from 1993 to 1996. Dr. Ira B. Tager and colleagues of the University of California, Berkeley, CA, conducted the first study, *Variability of Pulmonary Function Measures*, and the second study, *An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)*; and Dr. Patrick L. Kinney and colleagues of the University of Columbia, NY, conducted the third study, *An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)*. The following Research Report contains the three Investigators' Reports and a Commentary on the studies prepared by the Institute's Health Review Committee.

TABLE OF CONTENTS

Research Report Number 81

Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure

I. STATEMENT Health Effects Institute
This Statement, prepared by the HEI and approved by the Board of Directors, is a nontechnical summary of the Investigators' Report and the Health Review Committee's Commentary.

II. INVESTIGATORS' REPORTS
When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three outside technical reviewers and a biostatistician. The Report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

Part I: Variability of Pulmonary Function Measures

Ira B. Tager, Nino Künzli, Long Ngo, and John Balmes
Division of Public Health Biology and Epidemiology, and Division of Biostatistics and Information Science, School of Public Health, University of California, Berkeley, CA; Institute for Social and Preventive Medicine, Basel, Switzerland; and Division of Occupational and Environmental Medicine, University of California, San Francisco, CA

Abstract 1
Introduction 2
Specific Aims 3
Methods 4
  Sample Size Considerations and Recruitment of Subjects 4
  General Protocol 5
  Pulmonary Function Tests 5
  Analysis of Data 6
Results 7
Discussion 17
Conclusions 21
Acknowledgments 22
References 22
About the Authors 25
Abbreviations 25

Part II. An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)

Ira B. Tager, Nino Künzli, Fred Lurmann, Long Ngo, Mark Segal, and John Balmes
Division of Public Health Biology and Epidemiology, School of Public Health, and Division of Biostatistics and Information Science, University of California, Berkeley, CA; Institute for Social and Preventive Medicine, Basel, Switzerland; Sonoma Technology, Inc., Sonoma, CA; and Division of Occupational and Environmental Medicine, University of California, San Francisco, CA

Abstract 27
Introduction 28
Specific Aims 29
Methods 29
  Development of Questionnaires 29
  Study Subjects 31
  Implementation of Study Protocol 32
  Evaluation of Questionnaires 32
  Assignment of Exposure Values to Residential Locations 33
  Assignment of Individual Effective Exposures 34
  Pulmonary Function Data 37
  Data Management 38
  Statistical Analysis 38
Results 39
  General Results 39
  Reliability of Residential History 41
  Reliability of Activity Questions 43
Discussion 55
  Reliability of Questionnaire-Based Estimates of Lifetime Exposure to Ozone 55
  Preliminary Analysis of the Relation Between Estimated Lifetime Exposure to Ambient Ozone and Measures of Pulmonary Function 59
Conclusions 61
Acknowledgments 61
References 61
Appendix A. Questionnaires 64
Appendix B. Manufacturer's Documentation of Pulmonary Function Instrument (Available on Request) 70
Appendix C. Pulmonary Function Measurement Protocols and Quality Control Procedures 70
Appendix D. Plots of Regression Diagnostics for Regressions of Measures of Pulmonary Function on Standardized Estimated Lifetime Ozone Exposures 74
About the Authors 77
Publications Resulting from This Research 77
Abbreviations 78

(Continued on next page)

Part III. An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)

Patrick L. Kinney, Maneesha Aggarwal, Sergey V. Nikiforov, and Arthur Nadas
Division of Environmental Health Sciences, Columbia School of Public Health, New York, NY; Institute of Environmental Medicine, New York University Medical Center, Tuxedo, NY

Abstract 79
Introduction 79
Specific Aims 80
Methods 80
Data Retrieval and Processing 80
Interpolation of Ozone Concentrations 81
Activity History Questions 83
Long-Term Exposure Estimation 84
Quality Assurance 84
Results 85
Data Summaries 85
Interpolation of Ozone Concentrations 88
Reliability of the Activity History Questions 92
Long-Term Exposure Estimation 96
Quality Assurance 98
Discussion 98
Interpolation of Ozone Concentrations 99
Activity History Questions 100
Long-Term Exposure Estimation 101
Study Limitations 101
Study Design Implications 102
Conclusions and Suggested Areas for Future Research 103
Acknowledgments 103
References 103
Appendix A. Questionnaire 105
About the Authors 107
Publications Resulting from This Research 108
Abbreviations 108

III. COMMENTARY Health Review Committee

The Commentary on the Investigators' Reports is prepared by the HEI Health Review Committee and staff. Its purpose is to place the study into a broader scientific context, to point out its strengths and limitations, and to discuss the remaining uncertainties and the implications of the findings for public health.

Introduction 109
Scientific Background 110
Technical Evaluation of Dr. Tager's Reports 111
Objectives 111
Part I. Pulmonary Function Tests 112
Study Design 112
Results and Interpretation 113
Part II. Estimating Lifetime Ozone Exposure 113
Study Design 113
Results and Interpretation 114
Preliminary Study of Lung Function and Estimated Ozone Exposure 115
Conclusions 115
Technical Evaluation of Dr. Kinney's Report 115
Objectives and Study Design 115
Methods for Estimating Ozone Exposure 116
Key Findings 116
Interpretation 117
Developing and Testing a Questionnaire to Assess Activity History 117
Estimates of Long-Term Ozone Exposure, and the Variability of Ozone Levels over Time and Space 117
Design of Future Epidemiologic Studies 118
Conclusions 118
Discussion of the Tager and Kinney Studies 118
Acknowledgments 119
References 119

IV. RELATED HEI PUBLICATIONS 123

Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure

Part I: Variability of Pulmonary Function Measures

Ira B. Tager, Nino Künzli, Long Ngo, and John Balmes

ABSTRACT

The acute and subacute effects of ambient concentrations of ozone on lung function have been studied extensively in a variety of settings. Such studies generally have focused on measures of function that reflect either lung volumes or flows that are influenced by the physiology of large and small airways (e.g., forced expiratory volume in one second [FEV_1]*). Data from animal studies suggest that the effects of prolonged exposure to elevated ambient concentrations of ozone result in abnormalities in the centriacinar region of the lung; and dosimetry models for humans predict that long-term exposure to ozone could impact the same areas of the human lung. However, alterations in structure at this level of the lung are not well reflected by measuring FEV_1 until substantial structural changes have occurred. Measures of the lung function that reflect the functional mechanics of airways smaller than 2 mm in diameter are considered to be more relevant. At least one epidemiologic study has provided evidence that small-airway functions may be relevant to effects of prolonged exposure to environments with high concentrations of oxidants.

A considerable body of physiologic data has established that flow rates measured during the terminal portion of a maximum expiratory flow-volume (MEFV) curve are largely governed by airways smaller than 2 mm in diameter. A similar interpretation has been given to changes in the slope of phase III (ΔN_2) of the single-breath nitrogen washout (SBNW) curve. Despite the attractiveness of these measures in relation to airway physiology, some data suggest that measurements of flow via the terminal portions of MEFV and SBNW curves have much greater within-subject variability than forced vital capacity (FVC) and FEV_1. The present study was undertaken as part of a larger feasibility study to develop methods to study the effects of prolonged exposure to elevated ambient ozone levels on lung function in adolescents.

A convenience sample of 239 freshmen (ages 16–20 years) entering the University of California, Berkeley were recruited to participate in this protocol. All were lifelong residents of the San Francisco Bay Area or the Los Angeles Basin. Subjects were studied on two occasions five to seven days apart. At each test session, subjects performed up to eight forced expiratory maneuvers to produce three acceptable and reproducible MEFV curves by modified American Thoracic Society criteria. Tests of SBNW were then performed on the basis of detailed criteria for validity and reproducibility. Eight attempts to generate three curves were allowed. The ΔN_2 was obtained by a least-squares regression of nitrogen concentrations between the 750-mL and 1750-mL volume points. Instantaneous flow at 75% of expired volume ($FEF_{75\%}$), average flow between the 25% and 75% volume points ($FEF_{25\%-75\%}$), and ΔN_2 were the principal outcomes. Variance components were estimated with a nested random effects model with adjustments for important covariates.

The average within-subject coefficients of variation (± SD of distribution of means) for male subjects were: FEV_1 1.2 (± 0.8); $FEF_{25\%-75\%}$ 3.2 (± 2.3); $FEF_{75\%}$ 5.8 (± 5.0); and ΔN_2 17.9 (± 12.3); for female subjects they were: FEV_1 1.4 (± 0.9); $FEF_{25\%-75\%}$ 3.0 (± 2.2); $FEF_{75\%}$ 6.2 (± 5.2); and ΔN_2 19.9 (± 17.0). The variance attributed to test session was less than 1% for all measures. The percentages of variance due to within-subject variation for each measure (adjusted for sex, area of residence, ethnicity, and height) were: FVC 3.6%; FEV_1 3.0%; $FEF_{25\%-75\%}$ 5.2%; $FEF_{75\%}$ 8.9%; and ΔN_2 23.9%. Of all subjects tested, 234 (97.9%) could provide at least two acceptable MEFV curves, but only 218 (91.2%) could provide at least two acceptable SBNW curves. The results were unchanged by recent history of acute respiratory illness.

* A list of abbreviations appears at the end of the Investigators' Report.

This Investigators' Report is Part I of Health Effects Institute Research Report Number 81, which also includes *Part II: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)*, by Dr. Ira Tager and associates; *Part III: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)*, by Dr. Patrick Kinney and associates; a Commentary by the Health Review Committee on all three Investigators' Reports; and an HEI Statement about the research projects. Correspondence concerning the Part I Investigators' Report may be addressed to Dr. Ira Tager, School of Public Health, University of California, Berkeley, CA 94720-7360.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

This study has demonstrated that it is feasible to obtain flows from the middle and terminal portions of the MEFV curve at a sufficient degree of precision for use in epidemiologic studies of the effects of prolonged exposure to ozone on measures of lung function that reflect the physiology of peripheral airways. The optimal measure in terms of precision is $FEF_{25\%-75\%}$, although it is a less specific measure of small-airway physiology than $FEF_{75\%}$. Although $FEF_{75\%}$ can be less precisely measured than $FEF_{25\%-75\%}$, the decrease in precision is small and the additional costs in the efficiency of conducting cross-sectional and longitudinal studies should be low. Furthermore, both $FEF_{25\%-75\%}$ and $FEF_{75\%}$ can be obtained easily from the same forced expiratory maneuvers on computerized spirometers. On the other hand, ΔN_2 does not seem well suited for such studies because it provides a much less precise measure than those for flows. Furthermore, the SBNW test requires more complex equipment and subjects are less likely to be able to produce useable data. Moreover, the advantages of ΔN_2 data over data from the terminal portion of the MEFV curve have not been conclusively demonstrated.

INTRODUCTION

The acute and subacute effects of ambient concentrations of ozone on lung function have been studied extensively both in controlled chamber-exposure studies and in field studies of children and adults (Lippman 1989a,b; U.S. Environmental Protection Agency 1992b, 1995; Ostro 1993). The effects of long-term exposure to ambient concentrations of ozone on lung function have been evaluated, to a much lesser extent, by means of population-based epidemiologic studies (Detels et al. 1979, 1981, 1987, 1991; Stern et al. 1989, 1994; U.S. Environmental Protection Agency 1992b, 1995). With few exceptions (Detels et al. 1991; Keefe et al. 1991; Weinmann et al. 1995a,b,c), these human studies, especially the controlled chamber-exposure studies, focused on functional measures that relate to lung volumes, such as FVC and to a lesser extent FEV_1, and on parameters of lung mechanics that predominantly, or in part, reflect central airway physiology, such as FEV_1, specific airway resistance, and to some extent $FEF_{25\%-75\%}$ (Hyatt 1983). According to current understanding, the changes in lung volume measures are principally related to reflex reductions in vital capacity (Hazucha et al. 1989) and may not reflect pathophysiologic alterations that are perhaps more relevant to the long-term effects of ozone exposure or reflect the principal sites of ozone effect.

Studies in animals experimentally exposed to ozone at various concentrations and for varying periods of time suggest that the principal site of morphologic damage is the centriacinar region of the lung (junction of the conducting airways with the gas exchange regions) (U.S. Environmental Protection Agency 1986, 1992b; Collaborative Ozone Project Group 1995). Acute and chronic inflammation as well as remodeling have been observed in the centriacinar regions of exposed animals (U.S. Environmental Protection Agency 1992b, 1995). Of particular interest in terms of possible chronic effects of exposure is the concomitant inflammation (respiratory bronchiolitis) and remodeling in the centriacinar region, that is, changes in cell populations and interstitial collagen (U.S. Environmental Protection Agency 1995). Recent theoretical models of ozone dosimetry in humans suggest that when ozone is inhaled the maximum doses to the lung occur at the level of the terminal bronchioles in the centriacinar region (U.S. Environmental Protection Agency 1995). With increases in ventilation, there is a shift of ozone farther into the peripheral airways of the lung.

On the basis of experimental and theoretical dosimetric modeling data, Bates (1993) proposed an analogy between the effects of ozone on the human lung and those of cigarette smoke. The earliest lesions associated with cigarette smoking are those of a respiratory bronchiolitis that is similar in many ways to that observed in ozone-exposed animals (Niewoehner et al. 1974; Cosio et al. 1977; Saetta et al. 1994). Moreover, the changes of respiratory bronchiolitis are found in young smokers before changes in FEV_1 would be expected to be present (Niewoehner et al. 1974).

Studies of the correlation between lung pathology and function have shown a relation between abnormalities of the centriacinar region and a variety of measures of respiratory function (Wright et al. 1992). The most consistent associations have been with alterations of measures thought to reflect small airway physiology, such as flows from the midportion of MEFV curves, and especially parameters derived from SBNW curves (Wright et al. 1992). In controlled chamber-exposure studies, short-term exposures of humans to ozone concentrations in the range of 350 to 400 parts per billion (ppb) were associated with changes in functional measures related to alterations in small airways (Keefe et al. 1991; Weinmann et al. 1995a,b,c). Although its results have been controversial, at least one epidemiologic study of adolescents reported annual decrements in measures related to the small airways, such as flows at low lung volumes and ΔN_2 of the SBNW curves which were greater than the decrements for FEV_1 (Detels et al. 1987, 1991). This observation was particularly true for subjects under 25 years of age.

Several studies have demonstrated that lung function measures related to the state of the small airways (for

example, flows at low lung volumes derived from MEFV curves and ΔN_2) are abnormal in cigarette smokers even when there are no abnormalities in FVC and FEV_1 (Buist et al. 1973; Buist and Ross 1973; Berend et al. 1980; Nemery et al. 1981). Although some controversy remains about whether these early abnormalities are directly predictive of the decline of lung function observed in some smokers, the preponderance of data suggests that abnormalities of the small airways constitute an integral component of the obstructive airways disease of cigarette smokers (Bates 1989; Saetta et al. 1994). If the analogy offered by Bates is relevant to the investigation of the effects of long-term exposure to ambient concentrations of ozone, then measures of small airway function should be included routinely in epidemiologic studies of the effects of ozone on respiratory function.

A considerable body of physiologic data has established that flow rates measured during the terminal portion of a maximum forced expiratory maneuver, the maneuver used to generate FVC and FEV_1 (for example, $FEF_{75\%}$), are largely governed by the properties (geometry, compliance, and tethering effect of surrounding lung parenchyma) of airways smaller than 2 mm in diameter (Hyatt 1983). Maximum expiratory flow-volume curves are easily obtained from the highly standardized forced expiratory maneuvers that have been used in countless epidemiologic studies (American Thoracic Society 1987, 1991; Enright et al. 1991). The practicality of using gas washout tests for epidemiologic studies has been established (Buist and Ross 1973; Knudson et al. 1977; Detels et al. 1987; Teculescu et al. 1990). However, gas washout tests are more difficult to perform than forced expiratory maneuvers, and procedures for standardization are less widely published.

Substantial data are available on the between-subject variability of flows derived from the middle and terminal portions of the MEFV curve (small sample from an enormous body of published data: Knudson et al. 1976, 1983; Dockery et al. 1985). In contrast, relatively few data are available on the within-subject variability of parameters derived from FVC maneuvers (Burki et al. 1975; McCarthy et al. 1975; Rozas and Goldman 1982; Tweeddale et al. 1984; Enright et al. 1995). Even fewer data are available on within-subject variability estimates for adolescents and young adults, the study of whom would be of particular interest in relation to early ozone-related changes in small airway function that might be analogous to the early changes observed in cigarette smokers (Leeder et al. 1977; Hutchison et al. 1981). What data there are suggest that the within-subject variability of flow measures at middle and low lung volumes is two to three times greater than the variabilities of FVC and FEV_1 (McCarthy et al. 1975; Leeder et al. 1977; Hutchison et al. 1981).

Two large studies provided data on SBNW curves for adolescents (Adams et al. 1984; Teculescu et al. 1990); however, neither study provided data on within-subject and between-subject variability of ΔN_2. A substudy (Teculescu et al. 1987) provided some variability data for children 10 to 16 years of age. The mean individual coefficient of variation (CV) for ΔN_2 was 12.9% compared with 2.2% for vital capacity. Variability over two weeks was five-fold greater for ΔN_2 than for vital capacity (Teculescu et al. 1987). Hutchison and colleagues (1981) studied 20 adolescents aged 10 to 16 years and observed a CV for ΔN_2 of approximately 23% for measurements made over four days compared with CVs of 3% for FVC and 10% for $FEF_{25\%-75\%}$. A similar CV for ΔN_2 was provided by DeGroodt and coworkers (1984) for 39 subjects aged 14 to 16 years. Data also are available on the variability of parameters derived from SBNW curves in several small studies of older subjects (Becklake et al. 1975; Burki et al. 1975; Ducic et al. 1975; Marcq and Minette 1976). A study of young adults demonstrated an average within-subject CV of approximately 20% for ΔN_2 versus approximately 14% for $FEF_{75\%}$, 8% for $FEF_{25\%-75\%}$, and 2% to 3% for FEV_1 (McCarthy et al. 1975). A study of 13 adults estimated that the between-subject variability was between one and four times the within-subject variability for ΔN_2 depending on the number of tracings per subject used for the estimates (Becklake et al. 1975); within-subject variability accounted for 40% of the overall mean square error compared with 11.7% for vital capacity. Finally, data from a large population study (Knudson et al. 1977) provided an estimate of the between-subject CV of 125% for ΔN_2 over the age range 8 to 19 years and 57.5% over the age range 20 to 54 years.

Estimates of within-subject and between-subject variance are particularly important in studies in which small differences are likely between groups of individuals, or in longitudinal studies in which rates of change in function are of interest. Both of these situations are relevant considerations for any study on the relation between long-term exposure to various concentrations of ambient ozone and changes in lung function that increase individual risk of obstructive lung disease.

SPECIFIC AIMS

The present investigation was undertaken as part of HEI's Environmental Epidemiology Planning Project (Health Effects Institute 1994) to:

1. develop more precise estimates of within-subject variability for flows derived from the terminal part of the MEFV curve and ΔN_2 in adolescents and young adults;

2. determine the suitability of the SBNW test for epidemiologic studies in terms of protocol standardization and within-subject and between-subject variability; and
3. compare the relative variability of flows at low lung volumes derived from MEFV curves with ΔN_2.

This investigation was part of a larger feasibility study to evaluate epidemiologic methods for a study to determine whether or not long-term exposure to ambient concentrations of ozone in the Los Angeles Basin produced decrements or alterations in measures of small airway physiology in adolescents that are consistent with the hypothesis that long-term ozone exposure, especially early in life, can lead to chronic changes in lung function at the level predicted by animal studies and dosimetric models. The results of the relation between respiratory function and estimated ozone exposure in the overall feasibility study are the subject of Part II of this Research Report.

METHODS

All procedures carried out were approved by the Committee for the Protection of Human Subjects of the University of California, Berkeley, and required written informed consent from each student. All students received remuneration for participation.

SAMPLE SIZE CONSIDERATIONS AND RECRUITMENT OF SUBJECTS

Issues of time and the logistics of the planned protocol (see section below) limited the number of subjects who could be studied. Therefore, a sample size estimate was based on the precision considered desirable for estimates of within-subject and between-subject variance under the assumptions of a nested random effects model (subject, test session, and replicates) (Neter et al. 1985), and on the number of students who could be studied in a single school year (estimated to be approximately 200). The report of Becklake and coworkers (1975) provided the most relevant and complete data on within-subject and between-subject variance for ΔN_2. With these estimates and the derivation of the variance components from a random effects model, a simulation based on variable numbers of subjects was undertaken to determine the confidence limits around the Becklake estimates of within-subject and between-subject variances. Based on a sample of 200 subjects, the Becklake estimates could be rejected by the study with $\alpha = 0.05$ if within-subject and between-subject variances differed by 10% and 20%, respectively, from the Becklake estimates.

The choice of subjects was motivated by several considerations. First, the aim of a large epidemiologic study would be to study adolescents who could provide data relevant to estimating lifetime ozone exposure. An age range of 18 to 20 years was considered an optimal compromise in terms of data variability. In any study of adolescents, continued "growth" of lung function would be a source of variability that would need to be minimized in a follow-up study. Although some increase of lung volumes in males can continue into the early fourth decade (Tager et al. 1988), growth of lung function, especially flow at low lung volumes, is largely complete by age 17 in both males and females, and especially in females (Tager et al. 1988; Wang et al. 1993a,b). Minimizing effects of growth clearly has implications for reducing between-subject and between-"time" (within-subject) variance, the latter being of particular importance for a longitudinal study. The lower boundary of the age criterion could be reduced, especially for females, in whom lung function growth generally ends earlier.

Second, the study population for a large study would be students entering the University of California, Berkeley, who had lived their entire lives in selected areas of California, either the Los Angeles Basin (LAB) or the San Francisco Bay Area (SFBA). Convenience samples of subjects were recruited between August 1993 and December 1994. Advertisements were placed in print media likely to be read by students, and notices were posted in areas frequented by students.

Inclusion criteria were evaluated through the completion of standardized questionnaires (Eligibility Questionnaire and Residential History Form in Appendix A, which appears at the end of Part II). Initial criteria for inclusion were

1. age from 16 to 20 years;
2. lifelong nonsmoker (defined as not smoking as much as one cigarette per day for more than one year) and not smoking in the year before testing;
3. no history of asthma (this criterion was modified as described below); and
4. lifelong resident of LAB or SFBA (a large number of volunteers turned out to be immigrants of Asian or Pacific Islander descent who had come to California very early in childhood).

To recruit the desired sample in the time allotted for the study, the criteria had to be relaxed in some cases. In the case of asthma or wheeze symptoms, subjects were entered into the study if they reported a history of asthma or wheezing that was confined to early childhood and no symptoms of or medication for asthma in their teen years ($n = 25$). In the case of residence, students were included if their first residence outside LAB or SFBA did not extend past the first year of life.

GENERAL PROTOCOL

Subjects came to a laboratory site on the campus of the University of California, Berkeley. All subjects but two were tested on two occasions within five to seven days, at approximately the same time of day. Two subjects took the second test after 14 days. All second tests were within six hours of the time of day of the first test (median 15 minutes).

Upon arrival in the laboratory, students completed the Eligibility Questionnaire and the Residential History Form. The technician reviewed the forms with the student on completion, and the student's eligibility was determined at that point. If the student was eligible, he or she completed the remainder of a questionnaire developed as a separate part of this project (see Appendix A; the details of the larger questionnaire are the subject of Part II of this Research Report). Students then completed the Pulmonary Function Test (PFT) Eligibility Form (see Appendix A) about respiratory symptoms at the time of testing and over the previous three to seven days and about the consumption of caffeinated beverages. At the time of test session 2, the same procedures were followed, except that the general Eligibility Questionnaire was not readministered. Maneuvers to test forced expiratory volume were performed before the SBNW test for all subjects.

PULMONARY FUNCTION TESTS

Equipment

All pulmonary function testing was carried out using the 2100 System of SensorMedics Corp., Yorba Linda, CA. This system was specifically chosen because of software that permits the necessary visual quality control of flows for the SBNW test.

Forced Vital Capacity and Maximum Expiratory Flow-Volume Curves The performance characteristics of the 2100 System mass flow sensor are documented in Appendix B (which is available on request from the Health Effects Institute; see note at the end of Part II). Only MEFV curves were displayed, but the system provided direct feedback to the operator about American Thoracic Society standards for start-of-test (volume of extrapolation) and end-of-test (duration of exhalation and flow plateau). At the onset of exhalation, a vertical line appeared on the screen, which enabled the technician to determine when six seconds had elapsed from the start of the FVC maneuver. The end-of-test message appeared on the screen when the FVC maneuver had lasted at least six seconds and there had been zero flow for at least two seconds. These two criteria presented some difficulties for the subjects, so the end-of-test criteria were modified (see below). When each test was saved for evaluation, the "extrapolated" volume and total expiratory time were displayed, providing an opportunity for the technician to use this information in the evaluation of each maneuver performed by a subject.

Both MEFV and time-volume curves could have been printed for each test. However, the resolution of the time-volume curves was insufficient to allow visual inspection of the curve details. Therefore, only MEFV curves were routinely printed and saved in hard copy.

The system was calibrated each day before use in accordance with the instructions from the manufacturer (Appendix B). An automated calibration and verification procedure also was carried out each day, before the system was used. If the system was shut down at any time during a day, it was recalibrated and reverified before testing resumed. All calibrations were within the 3% of the calibration volume recommended by the manufacturer as the cutoff point for the need to recalibrate the system. All calibration data were printed and stored.

The 2100 System's output for parameters derived from the MEFV curve are automatically corrected to BTPS. At the start of each day, the barometric pressure was entered into the system, as required, from an aneroid barometer (No. p-410-477, Warren E. Collins, Braintree, MA) mounted in the laboratory. The accuracy of the barometer was checked periodically by comparing its pressure readings with those of a local weather service. Temperature was entered for the calibration and was reentered for each subject's test from a thermometer mounted next to the test equipment.

Single-Breath Nitrogen Washout Curves A fast-response nitrogen analyzer (response time less than 50 msec) is used by the 2100 System. The system permitted easy calibration of the analyzer using a test bolus of 100% oxygen (Appendix B). The analyzer was calibrated at least once each day at the start of testing. If the technician had any reservation about the performance of the system, recalibration was undertaken as needed. This latter situation was infrequent.

For the purposes of this study, the most significant feature of the 2100 System was its ability to provide a continuous, real-time display of expiratory flow during the SBNW test and boundary markers for a range of 300 to 600 mL/sec (Figure 1). The most critical part in the quality control of the SBNW test was the subject's ability to control expiratory flow. Flows that were too rapid led to an attenuation of the apex-to-base gradient in nitrogen on which the test is based (Anthonisen et al. 1970; DeGroodt et al. 1983). The system measured ΔN_2 automatically as the best-fit line between the 750-mL and 1,750-mL volume points of the SBNW curve.

Protocols

Maximum Expiratory Flow-Volume Protocol Detailed written instructions were provided for the technician, based on an adaptation of American Thoracic Society (1991) criteria (Appendix C, which appears at the end of Part II). In addition, from the data of Krowka and colleagues (1987), another criterion, based on peak expiratory flow rate (PEFR), was added to the American Thoracic Society acceptability criteria. Each subject was permitted up to eight attempts to produce three acceptable and reproducible tests. All tests were performed with the subject in the sitting position and using nose clips. Initial acceptability criteria were:

1. acceptable effort, as determined by the technician and by visual inspection of the MEFV curve;
2. no machine error message for extrapolated volume;
3. PEFR within 10% of maximum PEFR; and
4. end-of-test criteria of at least six seconds' duration and zero flow for two seconds.

Height was measured with the subject in stocking feet to the nearest one-half inch with a wall-mounted stadiometer (No. 1000, Country Technology, Gay Mills, WI) based on a protocol derived from the Anthropomorphic Standardization Reference Manual (Lohman et al. 1988) (Appendix C). Weight was measured in stocking feet to the nearest pound with a digital electronic scale (Thinner, Country Technology, Gay Mills, WI).

Early in the protocol, it was observed that these young, healthy subjects reached a zero flow point well before the six-second component of the end-of-test criterion. Review of the test performance and visual inspection of the MEFV and time-volume curves of the subjects indicated that tests that lasted for less than six seconds did represent maximal FVC maneuvers. Therefore, for the majority of the subjects, the principal end-of-test criterion was zero flow for two seconds.

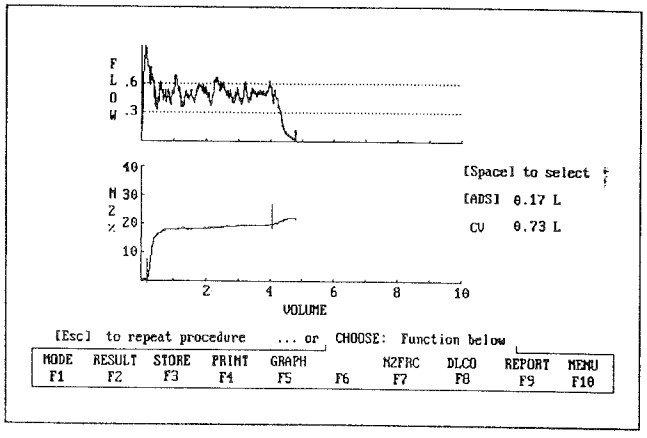


Figure 1. SensorMedics 2100 System screen image at the end of a SBNW test. Both expiratory flow and the expired nitrogen concentration are displayed in real time. Subjects were instructed to focus their attention on the flow curve.

Reproducibility criteria were FVC and FEV_1 values within 5% of maximum or within 100 mL (whichever was greater).

Single-Breath Nitrogen Washout Protocol Detailed written instructions for the performance of the SBNW test and the criteria for test acceptability were developed (Appendix C). The principal source for test criteria was "Suggested Standardized Procedures for Closing Volume" (Division of Lung Diseases, National Heart Lung and Blood Institute 1973). This document is the most comprehensive source of criteria for SBNW and was developed by Drs. R. Martin and P. Macklem and investigators who were participating in the Division of Lung Diseases contract program on the early diagnosis of chronic obstructive pulmonary disease in the early 1970s.

Before the study was implemented, the protocol was tested and the above criteria were modified to make the acceptable test criteria more stringent. Each subject was permitted one practice attempt after being given the test instructions and then up to eight further attempts to achieve three acceptable tracings. Throughout the test procedure, subjects were reminded constantly to monitor their expiratory flow with the use of the real-time visual expiratory flow tracing provided on a screen mounted in their direct line of vision. Examples of acceptable and unacceptable SBNW tests are provided in Appendix C.

To be acceptable, a test had to meet all of the following criteria:

1. after the first 500 mL of expired volume, flow between 300 and 600 mL/sec;
2. except for the first 500 mL of expiration, no expiratory flow transients above 600 mL/sec for a volume of at least 300 mL;
3. after the first 500 mL of expiration, no more than one flow transient above 600 mL/sec provided that this transient occurred over a volume of less than 300 mL;
4. no more than two flow transients below 300 mL/sec with a volume of at least 300 mL and no more than three such transients overall;
5. expired vital capacity not less than 5% of the best FVC value obtained during the FVC maneuvers; and
6. no "step" changes in N_2 concentrations with continued cardiogenic oscillations.

ANALYSIS OF DATA

Initially the components of variance for each of the tests of lung function were estimated by a nested random effects

analysis of variance (ANOVA) (Neter et al. 1985) that was implemented with the PROC NESTED procedure of SAS (SAS Institute 1991). The algorithm used is a moment-based algorithm that provides estimates of variance components and F tests for balanced data. Variance components can be obtained for unbalanced data, but no F test can be computed. This analysis considers individual, test session, and replicates at each test session as nested random effects (replicates within test sessions within individuals). The basic model (Neter et al. 1985) is:

$$y_{ijk} = \mu_{\cdot\cdot} + \alpha_i + \beta_{j(i)} + \in_{k(ij)},$$

where y_{ijk} is the kth PFT replicate at the jth test session for the ith subject; $\mu_{\cdot\cdot}$ is a constant; α_i represents constants that sum to 0 (effect of individuals); $\beta_{j(i)}$ represents constants that sum to 0 (effect of test sessions within individuals); and $\in_{k(ij)}$, represents independent error terms (effect of replicates within test sessions within subjects). All effects are assumed to be mutually uncorrelated.

Initially, analyses were carried out stratified by sex, race or ethnicity (Asian or Pacific Islander or other; "other" included the original questionnaire category choices of Caucasian [white], Hispanic, African American, Native American, and other), area of residence (LAB, SFBA), and reported history of chronic or acute respiratory symptoms.

Linear regression analyses were carried out to determine the need to adjust lung function measures for age and for height, or weight, or both height and weight, despite the very narrow range of ages of the subjects.

The final determination of the variance components was carried out as an analysis of a mixed linear model. The PROC MIXED procedure of SAS that employs a restricted maximum likelihood estimation procedure (SAS Institute 1992) was used. This model permits adjustment for covariates (for example, sex, race, area of residence, height, and expiratory time) as fixed effects and the evaluation of the random effects of individual, test session, and replicates within test session, as noted above. In addition, unbalanced data can be used, which makes it possible to include data from subjects who had fewer than three replicates at a session or missed one test session. Moreover, estimates of the standard error of each variance component are provided.

RESULTS

Of the 239 subjects between the ages of 17 and 21 years who participated in the pulmonary function protocols (Table 1), all but two (one female and one male) attended both test sessions. The median age of subjects was 19 years (Table 1); only 16 subjects were between 20 and 21 years.

Table 1. Selected Characteristics of Students Who Participated in the Pulmonary Function Tests

Characteristic	Males (n = 123)	Females (n = 116)	Total (n = 239)
Age [years]			
Median	19	19	19
25th–75th percentiles	18–19	18–19	18–19
Range	17–20	17–21	17–21
Ethnicity[a]			
White	40 (32.5)	29 (25.0)	69 (28.9)
Asian/Pacific Islander	66 (53.6)	68 (58.6)	134 (56.1)
Other[b]	17 (13.8)	19 (16.4)	36 (15.1)
Residence[a,c]			
Los Angeles Basin	64 (52.0)	69 (60.0)	133 (55.9)
San Francisco Bay Area	59 (48.0)	46 (40.0)	105 (44.1)
Height [cm]			
Median	175	163	170
25th–75th percentiles	170–180	157–168	163–175
Range	147–196	130–178	130–196

[a] Percentages of male, female, or total subjects are given in parentheses.

[b] Hispanic = 20; African American = 6; undefined other = 10.

[c] One female had missing data for area of residence.

Fifty-six percent of the subjects identified themselves as Asian or Pacific Islander. Somewhat more subjects were from LAB (56%) than from SFBA (44%). Thirty subjects had a first residence ($n = 27$) or first and second residences ($n = 3$) outside California. Of these, 20 (67%) were of Asian or Pacific Islander descent. In no case did the time from birth to arrival in LAB or SFBA exceed one year.

A past history of asthma (defined in the Methods section) was reported by 25 (10.5%) of the 239 subjects (Table 2). A past history of episodes of wheeze and shortness of breath with wheeze was reported by 17 (7.1%) and 12 (5%) of the subjects, respectively (Table 2). Two female subjects claimed to have smoked some cigarettes in the year before testing, but no subject reported having smoked as much as one cigarette per day for a year or 20 packs in a lifetime (Table 2). Forty subjects reported having smoked cigarettes at some time more than one year before testing, but none smoked more than the amounts stated previously. Seven subjects

Table 2. Selected Chronic Respiratory Symptoms and Smoking History of Subjects[a]

Symptoms and Smoking History	Males ($n = 123$)	Females ($n = 116$)	Total ($n = 239$)
Ever had asthma	14 (11.4)	11 (9.5)	25 (10.5)
Past episodes of wheeze	4 (3.3)	13 (11.2)	17 (7.1)
Past episodes of shortness of breath with wheeze	5 (4.1)	7 (6.0)	12 (5.0)
Smoked ≥ 1 tobacco cigarette/day for 1 year	0	0	0
Smoked 3 marijuana cigarettes/week for 6 months	0	0	0

[a] Percentages of male, female, or total subjects are given in parentheses.

Table 3. Selected Acute Respiratory Symptoms Reported at the Time of Pulmonary Function Testing[a]

Symptom Reported at Test Session	Males ($n = 123$)	Females ($n = 116$)	Total ($n = 239$)
Runny or stuffy nose previous week			
Session 1	13 (10.6)	6 (5.2)	19 (7.9)
Session 2	11 (8.9)	9 (7.7)	20 (8.3)
Cough in previous 72 hours			
Session 1	4 (3.3)	3 (2.6)	7 (2.9)
Session 2	4 (3.3)	0	4 (1.7)
Wheeze or whistling in chest in previous 72 hours			
Session 1	0	0	0
Session 2	1 (0.8)	0	1 (0.4)
Fever in previous 72 hours			
Session 1	0	0	0
Session 2	2 (1.6)	0	2 (0.8)
Cold or flu in last 7 days			
Session 1	14 (11.4)	15 (12.9)	29 (12.1)
Session 2	5 (4.1)	3 (2.6)	8 (3.3)
Sought medical care in previous week			
Session 1	0	2 (1.7)[b]	2 (0.8)
Session 2	0	0	0

[a] Percentages of male, female, or total subjects are given in parentheses.

[b] No inhaled bronchodilator or steroid medications were prescribed.

(five female and two male) reported having smoked marijuana in the year before testing, but no subject had smoked as many as three marijuana cigarettes per week for as long as six months (Table 2).

The acute respiratory symptom most frequently reported at the time of testing was the occurrence of a cold or the "flu" in the previous seven days (12% test session 1, 3% test session 2; Table 3). Eight percent of students reported a runny or stuffy nose in the previous week at both test sessions 1 and 2 (Table 3). Cough in the preceding 72 hours was reported by 3% and 2% of subjects at test sessions 1 and 2, respectively, and only one subject reported wheezing in the 72 hours preceding testing (Table 3). Only two subjects reported seeking medical care in the week before testing (two females at test session 1). In neither case was an inhaled bronchodilator or an inhaled steroid drug prescribed. Most subjects (84%) reported drinking caffeinated beverages; however, only 3.3% consumed a caffeinated beverage in the 24 hours before testing.

Subjects were more likely to produce three acceptable replicates for the MEFV curves than for the SBNW curves (Table 4). In addition, there was evidence of a small learning effect between test sessions 1 and 2, in terms of the number of acceptable tests produced by each subject. For the MEFV curves 89% of subjects provided three acceptable replicates at test session 1 and 95% at test session 2 (Table 4). The comparable percentages for the SBNW test were 78% and 84%, respectively.

As noted above, subjects had considerable difficulty sustaining the minimum six-second expiratory time required for the MEFV curves. The median expiratory time for the 679 MEFV curves available for analysis for test session 1 was 3.6 seconds (25th to 75th percentiles 2.5 to 5 seconds; range 1.1 to 10.6 seconds) (Figure 2). Of these curves, 177 (26.1%) represented at least six seconds of expiration. There was a small, but significant correlation between FVC and expiratory time (Spearman correlation = 0.145; p values are not provided, as the data contain repeated measures for each subject), and there was a moderate negative correlation between $FEF_{75\%}$ and forced expiratory time (Spearman correlation = −0.422, p = 0.001) (Figure 3). Two possible explanations can be offered for this observation.

One explanation is that this is the pattern of correlations that would be expected if subjects were making a maximum effort. As subjects made greater efforts, expiratory time would diminish as a larger fraction of volume was expired over a shorter period of time; and flows would increase. This increase in effort would result in greater gas compression (Ingram and Schilder 1966; Krowka et al. 1987), which in turn could lead to the slightly lower FVC values observed with shorter expiratory times.

The other explanation is that some FVC maneuvers may have been terminated slightly prematurely. The flow-sensing device used by the SensorMedics 2100 System is based on mass flow and not volumetric flow (technical documentation from SensorMedics Corp. is presented in Appendix B, which is available on request from the Health Effects Institute; see note at end of Part II). Therefore, the measured volume (integrated from flow), in theory, should not be affected by gas compression. In FVC maneuvers that terminated slightly prematurely, flows at specific lung volumes would be measured at slightly higher lung volumes than if the maneuver had been continued slightly longer. This would tend to give higher values for the flows and the negative correlations between flows and volume.

Table 4. Distribution of Replicate Tests at Each Test Session[a]

	Number of Replicates			
Test Session	0	1	2	3
MEFV Curves				
Session 1 (n = 239)	3 (1.3)	6 (2.5)	17 (7.1)	213 (89.1)
Session 2 (n = 237)	2 (0.8)	1 (0.4)	10 (4.2)	224 (94.5)
SBNW Curves				
Session 1 (n = 239)	16 (6.7)	14 (5.9)	23 (9.6)	186 (78.2)
Session 2 (n = 237)	8 (3.4)	13 (5.5)	16 (6.8)	200 (84.4)

[a] Values in parentheses indicate the percentage of n subjects at the test session.

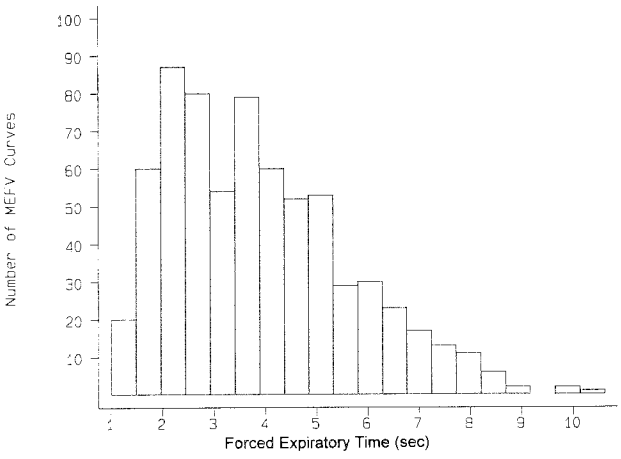


Figure 2. Distribution of forced expiratory time in seconds for 679 individual MEFV curves obtained at test session 1. Each subject contributed one to three curves for this analysis.

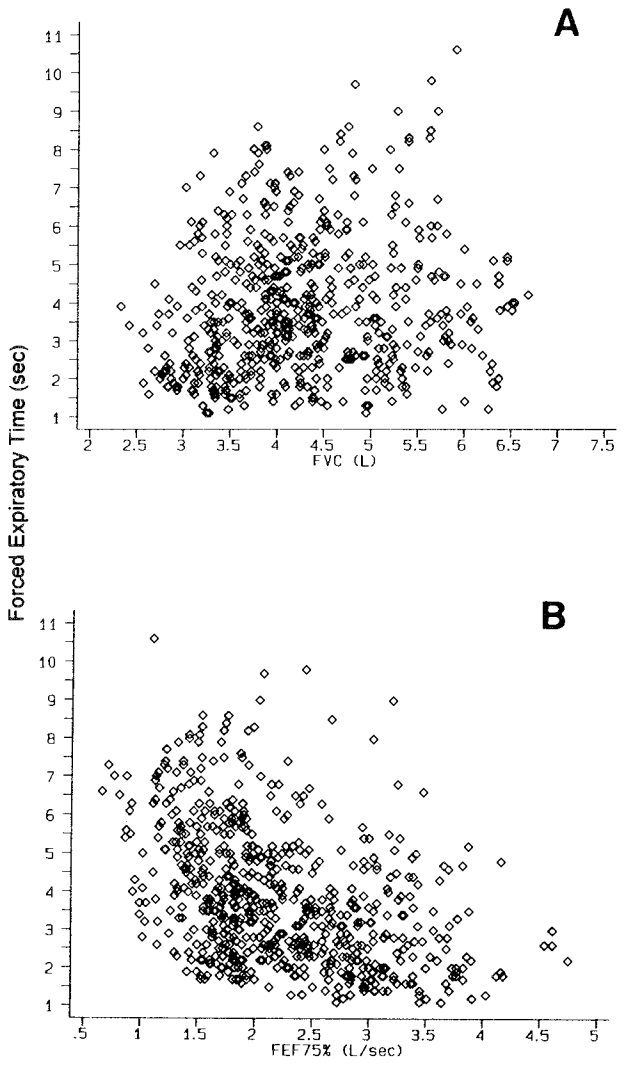


Figure 3. Relation between (A) forced expiratory time and FVC and (B) forced expiratory time and $FEF_{75\%}$. Each subject contributed one to three curves for this analysis. The Spearman correlations for panels A and B are 0.145 and −0.422, respectively. No p values are given for the Spearman correlations because of the multiple observations per subject.

Nonetheless, all of the ANOVA components that adjusted for forced expiratory time were unchanged from those analyses in which the effects of forced expiratory time were not considered. Therefore, it is highly unlikely that the results have been influenced to any meaningful degree by the above relations; and the effect of forced expiratory time is not considered further.

The sex-specific, overall distributions of the individual mean pulmonary function measures, based on test session 1, are provided in Table 5; the accompanying CVs are presented in Table 6. Across both sexes (Figure 4), 95% of the CVs for FVC and FEV_1 were less than 3%. For $FEF_{25\%-75\%}$, 95% of CVs were less than 8%; and for $FEF_{75\%}$, the comparable percentage was 14.5%. For both males and females ΔN_2 was substantially more variable than the flows derived from the MEFV curves (Table 6). The 95th percentile for ΔN_2 CVs was 51%, and 50% of the CVs for ΔN_2 were greater than the 95th percentile value for $FEF_{75\%}$ (14.2%). The CVs were weakly correlated with the mean levels for each of the volumes and flows derived from the MEFV curves (Figure 5). However, there was a moderate negative correlation between the CV for ΔN_2 and the individual mean values (Figure 5; $r = -0.37$, $p = 0.0001$).

The differences between test sessions in the mean values of the flows derived from the MEFV curves were small (Table 7). The median difference for both FVC and FEV_1 was 0.10 L overall, which represented 3% of the mean for both measures for both sexes. The overall median difference for $FEF_{25\%-75\%}$ was 0.22 L/sec, which represented 6% of the female and 7% of the male means. The overall median difference for $FEF_{75\%}$ was 0.17 L/sec, which represented 10% of the female and 11% of the male means. The overall median difference for ΔN_2 was 0.20 (Table 7), which represented 24% of the female and 21% of the male means.

Overall, there was a weak negative correlation between each individual's mean $FEF_{25\%-75\%}$ and the mean ΔN_2 (Pearson correlation = −0.15; $p = 0.03$). The correlation between $FEF_{75\%}$ and ΔN_2 was even weaker (Pearson correlation = −0.09; $p = 0.19$). For both $FEF_{25\%-75\%}$ and $FEF_{75\%}$, the correlation with ΔN_2 was somewhat stronger for males than for females (Figure 6).

A preliminary analysis was undertaken to determine the extent to which the report of chronic or acute respiratory symptoms affected the variance of the different tests. Subjects were divided into four categories based on the report of symptoms on either the Eligibility Questionnaire or the

Table 5. Overall Distribution of Individual Mean Pulmonary Function Measures[a]

	Males ($n = 123$)[b]	Females ($n = 112$)[b]
FVC [L]	4.82 ± 0.74	3.56 ± 0.52
FEV_1 [L]	4.17 ± 0.63	3.10 ± 0.43
FEV_1/FVC [%]	86.7 ± 6.1	87.5 ± 5.5
$FEF_{25\%-75\%}$ [L/sec]	4.65 ± 1.07	3.67 ± 0.83
$FEF_{75\%}$ [L/sec]	2.48 ± 0.74	1.90 ± 0.57
ΔN_2 [$\%\Delta N_2$/L]	1.02 ± 0.40	1.12 ± 0.51

[a] Data are reported as means of individual mean values ± SD of distribution of means.

[b] n values indicate subjects with valid observations. For ΔN_2, $n = 115$ males and $n = 108$ females.

Table 6. Overall Distribution of Individual Coefficients of Variation (Measured in %) for Pulmonary Function Measures

	Males (n = 121)[a]	Females (n = 109)[a]
FVC		
Mean of means[b]	1.35 ± 0.99	1.28 ± 0.80
Range	0.00–7.52	0.00–4.07
1 SD[c]	0.07	0.05
FEV_1		
Mean of means	1.20 ± 0.76	1.35 ± 0.87
Range	0.14–3.88	0.16–4.98
1 SD	0.05	0.04
$FEF_{25\%-75\%}$		
Mean of means	3.20 ± 2.26	3.03 ± 2.22
Range	0.00–12.01	0.31–10.98
1 SD	0.14	0.11
$FEF_{75\%}$		
Mean of means	5.80 ± 4.95	6.18 ± 5.14
Range	0.00–33.96	0.30–37.40
1 SD	0.14	0.12
ΔN_2		
Mean of means	17.90 ± 12.33	19.85 ± 16.97
Range	0.00–58.08	0.00–92.49
1 SD	0.16	0.19

[a] n values indicate subjects with valid observations. For ΔN_2, n = 107 males and n = 104 females.

[b] The mean (measured in %) of individual, unadjusted mean values ± SD of distribution of means.

[c] The mean value of 1 SD in the units of each specific measure.

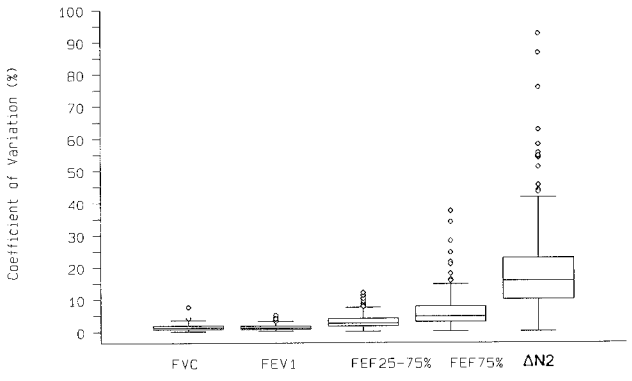


Figure 4. Box-plots of distributions of coefficients of variation around individual mean values for each measure of lung function. The middle bar in each box is the median, and the bottom and top ends of the box are the 25th and 75th percentiles of the distributions. Lines extending from the box have the approximate interpretation as the bounds of ± 2 SD. Diamonds indicate data points that have the approximate interpretation of ± 3 SD.

PFT Eligibility Form administered at each test session. No symptoms were reported on either questionnaire by 134 (56.1%) of the subjects, 59 (24.7%) reported at least one symptom on the Eligibility Questionnaire, 33 (13.8%) reported at least one symptom on the PFT Eligibility Form at the time of testing, and 13 (5.4%) reported symptoms on both questionnaires.

In these preliminary analyses, no adjustments were made for sex, ethnicity, height, or area of residence, none of which affected the estimates of the variance components (see below). The report of symptoms had virtually no effect on the magnitude of the variance components for any measure of pulmonary function (Table 8). The percentage of variance of FEV_1 contributed by test session ranged between 1.5% and 1.8%; the within-subject percentage of variance was 0.5% for all subject groups. The percentage of variance of $FEF_{25\%-75\%}$ contributed by test session ranged between 3.6% and 3.8%, and within-subject variability ranged between 2.0% and 2.2%. Percentage ranges for $FEF_{75\%}$ (5.3% to 6.1% and 4.5% to 4.8%) and ΔN_2 (7.4% to 8.8% and 15.6% to 16.7%) also were quite narrow. In view of this lack of effect of symptom reporting on variance components, all further analyses excluded consideration of symptoms.

A series of analyses were undertaken to determine the effects of sex, ethnicity, and area of residence on the components of variance. There was no significant difference in the distribution of males and females between LAB and SFBA, although more males did come from SFBA relative to females (56.2% males and 43.8% females from SFBA; $\chi^2_{(1)} = 1.53$, $p = 0.22$). However, subjects who listed their ethnicity as Asian or Pacific Islander were significantly more likely to be residents of SFBA (66.7% SFBA versus 48.1% LAB; $\chi^2_{(1)} = 8.20$, $p = 0.004$). Males and females were equally likely to be of Asian or Pacific Islander ethnicity (54.3% males versus 58.3% females; $\chi^2_{(1)} = 0.43$, $p = 0.51$). Variance components were very similar between the sexes and between areas of residence for measures derived from the MEFV curves and for ΔN_2 (Table 9).

In the case of ethnicity, variance components were very similar for FEV_1, $FEF_{25\%-75\%}$ (Table 9), and FVC (data not shown). In each case, for subjects of Asian or Pacific Islander ethnicity, the variability between test sessions and the within-subject variability were slightly greater. There was less similarity for $FEF_{75\%}$ and for ΔN_2, but there was no consistency in the direction of the differences (Table 9). The large difference in the percentage of within-subject variance for ΔN_2 (15.1% Asian or Pacific Islander versus 25.5% other) is more likely to be due to the inherent variability of this test than to the heterogeneity of subjects in the "other" category (69 white, 30 Hispanic, 6 African American, and 10 other), as the direction of the difference is opposite to that observed for $FEF_{75\%}$, which also is a measure of small airway function.

The overall estimation of the components of variance was based on a mixed linear model with area of residence, sex, ethnicity, and height as fixed effects and test session and individuals as random effects. Once height was included in the model, age was never a significant factor and therefore was not included. Area of residence was not a significant factor for any of the estimates of variance components of lung function but was retained for all adjusted models. As expected, female sex was associated with lower levels of parameters derived from the MEFV curves. There

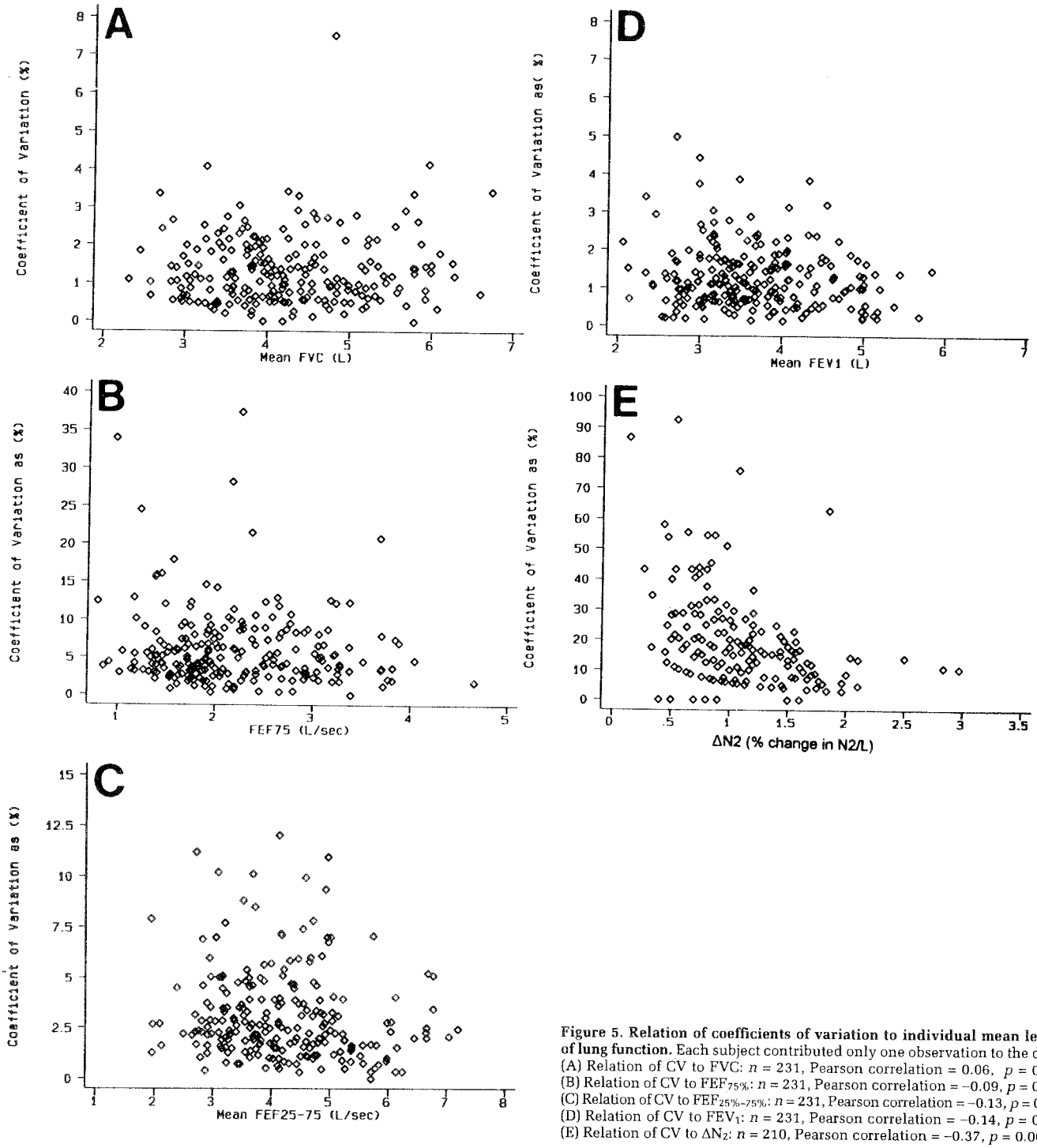


Figure 5. Relation of coefficients of variation to individual mean levels of lung function. Each subject contributed only one observation to the data. (A) Relation of CV to FVC: $n = 231$, Pearson correlation = 0.06, $p = 0.37$. (B) Relation of CV to $FEF_{75\%}$: $n = 231$, Pearson correlation = −0.09, $p = 0.16$. (C) Relation of CV to $FEF_{25\%-75\%}$: $n = 231$, Pearson correlation = −0.13, $p = 0.05$. (D) Relation of CV to FEV_1: $n = 231$, Pearson correlation = −0.14, $p = 0.03$. (E) Relation of CV to ΔN_2: $n = 210$, Pearson correlation = −0.37, $p = 0.0001$.

Table 7. Absolute Differences Between Test Sessions 1 and 2 in Mean Values for Pulmonary Function Measures

Value	FVC [L]	FEV_1 [L]	$FEF_{25\%-75\%}$ [L/sec]	$FEF_{75\%}$ [L/sec]	ΔN_2 [% ΔN_2/L]
n [a]	234	234	234	234	218
Mean ± SD	0.14 ± 0.14	0.12 ± 0.10	0.26 ± 0.23	0.23 ± 0.23	0.24 ± 0.24
Median	0.10	0.10	0.22	0.17	0.20
25th–75th percentile	0.04–0.19	0.05–0.16	0.09–0.36	0.05–0.30	0.10–0.30
Range	0.00–1.33	0.00–0.62	0.00–1.38	0.00–1.63	0.00–1.83

[a] Number of subjects with at least two acceptable replicates at both test sessions.

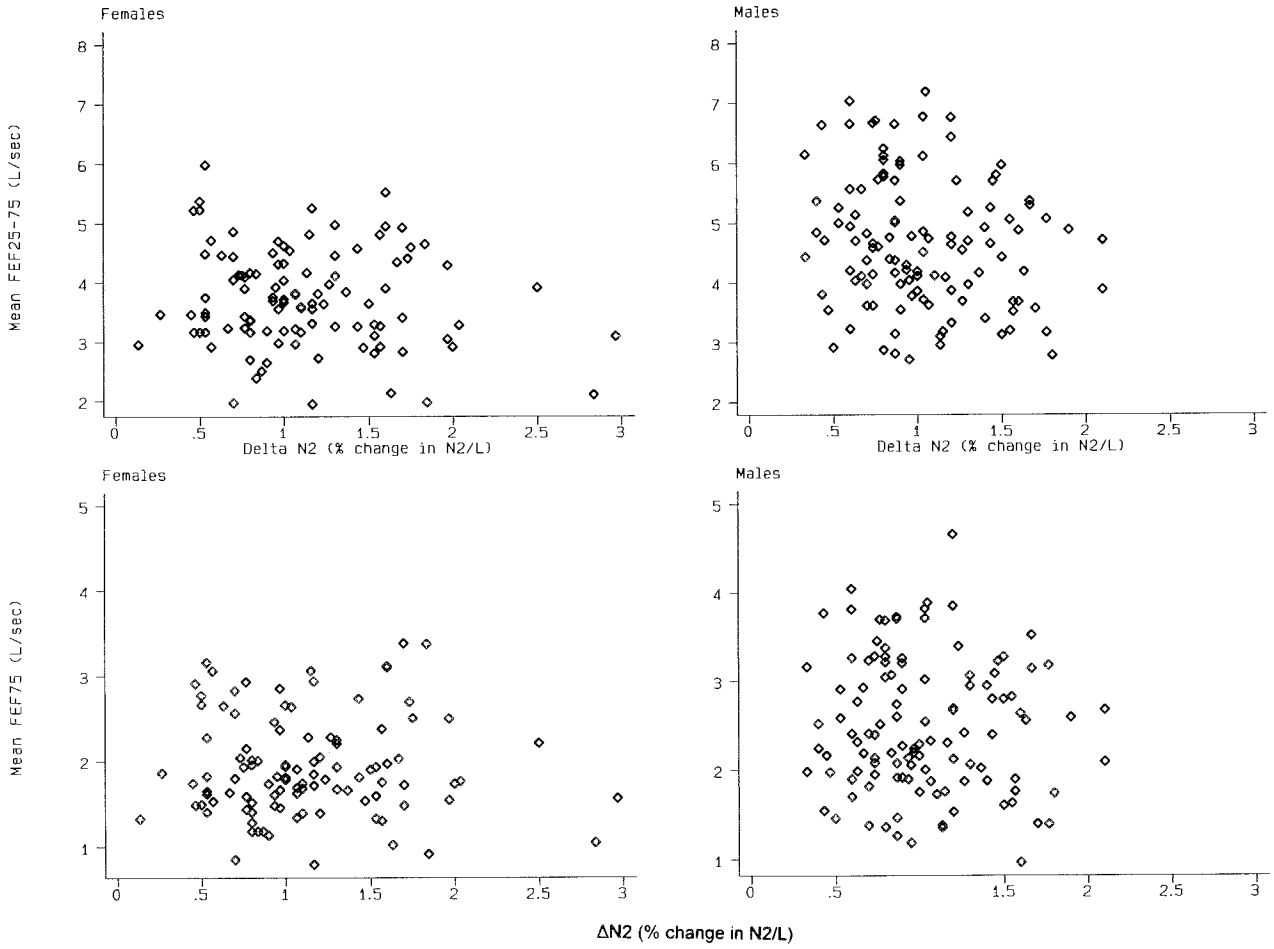


Figure 6. Sex-specific relation between individual mean levels of (Top) ΔN_2 and $FEF_{25\%-75\%}$ and (Bottom) ΔN_2 and $FEF_{75\%}$. (Top) Pearson correlation for females = −0.13; for males = −0.18. (Bottom) Pearson correlation for females = −0.01; for males = −0.07.

was not a significant sex difference for ΔN_2. Ethnicity was not significantly associated with $FEF_{25\%-75\%}$ or $FEF_{75\%}$, but subjects with Asian or Pacific Islander ethnicity had significantly lower levels of FVC and FEV_1 and a higher value for ΔN_2.

Table 10 presents the estimates of the components of variance for each measure of lung function after adjustment for area of residence, sex, ethnicity, and height. In all cases, the percentage of variance contributed by test session was less than 1%. For FVC and FEV_1, the variance due to within-subject variation was 3.6% and 3.0%, respectively, when test session variance was not explicitly controlled in the model. For $FEF_{25\%-75\%}$ and $FEF_{75\%}$, the comparable within-subject variance was 5.4% and 9.0%, respectively. In contrast, the within-subject variance for ΔN_2 was 23.9%.

Table 11 provides standard errors for the variance estimates from the model in which test session was not included. As most studies do not have short-interval test-retest data, these estimates of precision are most relevant (and are essentially identical to those obtained from models in which the effects of test session are included). Estimates of the between-subject variance components were highly precise. For all measures of function, the between-subject variance estimate was at least 10-fold greater than the standard error of the estimate, and was at least 20-fold greater in the case of the within-subject variance estimates.

Table 12 provides estimates of the CVs for all subjects (between-subject CV). Between-subject CVs based on single maximum values for each measure of function (Table 12), such as are often presented in epidemiologic studies, are very similar to those obtained from the analysis that uses all of the replicates and adjusts for differences in ethnicity, height, and area of residence for the measures derived from the MEFV curve. For ΔN_2, the between-subject CV is sensitive to the method by which the variance is estimated.

Table 8. Effect of Symptoms on Components of Variance for Selected Pulmonary Function Measures[a]

	Model Restricted To			
	All Subjects (n = 235)	Subjects Without Symptoms (n = 131)	Subjects Without Symptoms and Subjects with Symptoms on Test Session Questionnaire (n = 135)	Subjects Without Symptoms and Subjects with Symptoms on Either Questionnaire (n = 225)
FEV_1				
Between subjects	97.7	97.8	97.9	97.8
Between sessions	1.8	1.5	1.6	1.7
Within subject	0.5	0.5	0.5	0.5
$FEF_{25\%-75\%}$				
Between subjects	94.1	94.1	94.3	94.3
Between sessions	3.8	3.7	3.6	3.6
Within subject	2.1	2.2	2.1	2.0
$FEF_{75\%}$				
Between subjects	90.3	89.0	90.2	90.2
Between sessions	5.2	6.1	5.3	5.3
Within subject	4.5	4.8	4.6	4.5
ΔN_2				
Between subjects	75.9	76.4	74.6	76.0
Between sessions	8.3	8.0	8.8	7.4
Within subject	15.8	15.6	16.7	16.6

[a] Variance components were estimated with nested random effects ANOVA (PROC NESTED procedure of SAS) and without adjustment for potential covariates; data for FVC are not presented because they were very similar in magnitude to those for FEV_1. For each group, n values reflect the number of subjects who contributed MEFV curves. Values are presented as the percentage of total variance; limited to subjects with more than one replicate at each test session.

Table 9. Effect of Sex, Ethnicity, and Area of Residence on Components of Variance for Selected Pulmonary Function Measures[a]

	Sex		Ethnicity		Area of Residence	
	Male	Female	Asian/Pacific Islander	Other	Los Angeles Basin	San Francisco Bay Area
FEV_1						
Between subjects	95.7	94.6	97.1	97.9	97.3	98.1
Between sessions	3.4	4.0	2.3	1.6	2.1	1.4
Within subject	0.8	1.3	0.6	0.5	0.5	0.5
$FEF_{25\%-75\%}$						
Between subjects	92.6	92.4	92.9	95.0	94.2	93.9
Between sessions	4.8	4.8	4.3	3.4	3.8	3.9
Within subject	2.5	2.8	2.7	1.6	2.0	2.2
$FEF_{75\%}$						
Between subjects	88.2	88.9	87.3	93.1	89.5	91.1
Between sessions	6.7	4.8	7.4	3.1	6.1	4.2
Within subject	4.8	6.3	5.3	3.8	4.5	4.7
ΔN_2						
Between subjects	72.3	77.8	74.0	67.1	75.1	76.1
Between sessions	9.1	7.9	10.9	7.3	7.7	9.1
Within subject	18.5	14.3	15.1	25.5	17.1	14.9

[a] Variance components were estimated with nested random effects ANOVA (PROC NESTED procedure of SAS) and without adjustment for potential covariates; data for FVC are not presented because they were very similar in magnitude to those for FEV_1. Values are presented as the percentage of total variance; limited to subjects with more than one replicate at each test session.

Table 10. Components of Variance of Pulmonary Function Measures Adjusted for Sex, Ethnicity, Area of Residence, and Height[a]

Component of Variance	FVC	FEV_1	$FEF_{25\%-75\%}$	$FEF_{75\%}$	ΔN_2
Test session	0.0	0.1	0.7	0.2	0.0
Between subjects	96.0 (96.3)	96.8 (97.0)	95.0 (94.6)	91.1 (91.0)	76.0 (76.1)
Within subject (between replicates)	4.0 (3.6)	3.2 (3.0)	5.2 (5.4)	8.9 (9.0)	23.9 (23.9)

[a] Variance components were estimated with mixed linear model (PROC MIXED procedure of SAS). Values are presented as the percentage of total variance; values in parentheses reflect the percentage of total variance from the model with effect of test session unspecified.

Table 11. Standard Errors of Variance Components Estimates for Pulmonary Function Measures Adjusted for Sex, Ethnicity, Area of Residence, and Height[a]

	FVC		FEV_1		$FEF_{25\%-75\%}$		$FEF_{75\%}$		ΔN_2	
Component of Variance	Variance Estimate	SEE	Variance Estimate	SEE	Variance Estimate	SEE	Variance Estimate	SEE	Variance Estimate	SEE
Test session	0.000	NA	0.003	0.0004	0.007	0.009	0.0008	0.001	0.000	NA
Between subjects	0.378	0.036	0.279	0.026	0.905	0.084	0.437	0.041	0.166	0.017
Within subject (between replicates)	0.016	0.0007	0.009	0.0004	0.048	0.002	0.043	0.002	0.052	0.002

[a] Variance components were estimated with mixed linear model (PROC MIXED procedure of SAS). Values given are the variance estimate and the standard error of the estimate (SEE). NA = not applicable.

Table 12. Between-Subject Coefficients of Variation for Pulmonary Function Measures Adjusted for Sex, Ethnicity, Area of Residence, and Height[a]

	Males	Females
FVC		
CV based on total adjusted variance from mixed model	14.9	14.2
CV based on between-subject variance from mixed model	14.6	14.0
CV based on single maximum value from each subject	15.5	14.7
FEV_1		
CV based on total adjusted variance from mixed model	14.6	14.0
CV based on between-subject variance from mixed model	14.4	13.8
CV based on single maximum value from each subject	15.1	13.8
$FEF_{25\%-75\%}$		
CV based on total adjusted variance from mixed model	23.6	25.6
CV based on between-subject variance from mixed model	23.0	24.9
CV based on single maximum value from each subject	22.6	22.7
$FEF_{75\%}$		
CV based on total adjusted variance from mixed model	35.4	36.6
CV based on between-subject variance from mixed model	33.8	34.9
CV based on single maximum value from each subject	29.5	31.4
ΔN_2		
CV based on total adjusted variance from mixed model	37.2	36.1
CV based on between-subject variance from mixed model	32.1	31.7
CV based on single maximum value from each subject	36.6	42.6

[a] Adjusted means and estimates of variance were derived from a mixed linear model (PROC MIXED procedure of SAS), and are presented as percentages.

DISCUSSION

The subjects selected for this study represent a convenience sample of adolescents who might be considered as subjects for a study on the effects of lifetime exposure to ambient ozone concentrations on measures of lung function that reflect the major site of deposition of ozone in the lung (small airways). We selected subjects who had characteristics that would maximize our ability to distinguish the effects of ambient air pollution from the effects of other factors, such as a history of smoking tobacco or other materials (for example, marijuana), or the presence of active asthma, any of which could lead to alterations in the distribution of levels and variability measures of small airway function.

The overall lifetime 10.5% prevalence of asthma in this sample (Table 2) is similar to that observed in a prospective study of children and adolescents over a range of ages that includes the age distribution of the current study subjects (Carey et al. 1996). No subject in the present study had had symptomatic asthma since childhood, and no subject had smoked as much as one cigarette a day for more than one year. As the questionnaire that was used to evaluate the subjects was a test instrument for a companion feasibility study on the assessment of lifetime exposure to ambient ozone, data for passive exposure to the products of cigarette tobacco smoke (either prenatal or postnatal) were not evaluated. Therefore, any small effect of this exposure on variability is not accounted for in this analysis. Because passive exposure to tobacco smoke products is associated with small effects on lung function (U.S. Environmental Protection Agency 1992a), it is possible that the adjusted estimates presented for between-subject variances may be slightly larger than estimates that reflect adjustment for such passive exposure.

Although the protocol was designed to minimize extrinsic factors that might affect the components of variance, subjects who may have experienced acute respiratory events within the week before each test session were not excluded, nor were their test sessions postponed (Table 3). This strategy may have increased slightly both the between-subject and within-subject variances, although the data presented do not provide strong support for this possibility (Table 8 and see below). The strategy reflects the very realistic study situation in which it is not feasible or desirable to exclude subjects or postpone testing on this basis, due to the frequency of such events (loss of subjects and difficulty of study planning) and to the unwillingness of subjects to reschedule test sessions. These variance estimates provide more realistic estimates for study planning than if a more "purist" strategy had been followed. Therefore, the variability estimates that have been derived are those to be expected in a typical adolescent population without known pulmonary disease, with minimal exposure to tobacco products through personal use, and subject to the usual acute respiratory events that are known to have transient effects on lung function at the time of testing (Picken et al. 1972; Blair et al. 1976; Leeder et al. 1977; Hall et al. 1978).

The principal measures of lung function that have been selected for evaluation are those that reflect the function of small peripheral airways—$FEF_{75\%}$ and to a lesser extent $FEF_{25\%-75\%}$ and ΔN_2 (Cosio et al. 1977; Petty et al. 1980; Hyatt 1983; Bates 1992). The physiologic underpinnings for the flows at low lung volumes are generally accepted to be well understood (Hyatt 1983). In contrast, some uncertainty exists about the interpretation of SBNW curves. Paiva and colleagues (Muylem et al. 1992) failed to find a relation between ΔN_2 and pathology of the respiratory bronchioles. On the basis of theoretical models, these authors suggested that interregional convection-dependent inhomogeneities (related to gravity-dependent pleural pressure gradients and inhomogeneous elastic recoil of the lung) and the interaction of diffusion and convection at airway branch points are responsible, in part, for some of the variation in ΔN_2 (Paiva and Engel 1987). Active gas exchange also has been suggested to affect ΔN_2 even at rest (Cormier and Belanger 1981).

Nonetheless, the general consistency of the association between alterations in ΔN_2 and small airway pathology observed in other studies (Bates 1992) makes this measure of potential interest. Furthermore, although hampered by a number of methodologic problems, the UCLA population studies of chronic obstructive pulmonary disease generated data showing that ΔN_2 was a more sensitive indicator of oxidant and other air pollutant effects in children and adolescents followed for five to six years than were flows derived from the terminal portion of the MEFV curve (Detels et al. 1987, 1991). This is in contrast to data from a study of 92 children, aged 10 to 16 years, in whom ΔN_2 was less able to discriminate passive exposure to parental smoking than was instantaneous flow at 50% of FVC ($FEF_{50\%}$), a difference largely related to the greater variance of ΔN_2 (Teculescu et al. 1986).

Relatively few data are available from population-based studies of the effects of chronic exposure to ambient ozone on measures that may relate to events at the level of presumed ozone-induced small airway pathology. One large population-based study in Canada of children aged 7 to 11 years found no overall association between residence in a high-oxidant environment and level of $FEF_{25\%-75\%}$. Among

the asthmatic subjects, there was a 6% reduction in the $FEF_{25\%-75\%}$ level for those exposed to the high-oxidant environment, but the difference did not achieve statistical significance (Stern et al. 1994). Kinney and coworkers (1992) studied 154 cadets entering West Point and found lower levels of $FEF_{25\%-75\%}$ in those whose permanent residence was in a high-oxidant environment on the West Coast of the United States. The differences were larger (based on residuals from linear regression) than for FVC and FEV_1 but failed to reach statistical significance owing to the much larger residual, between-subject variability. The only data that relate to long-term ozone effects on ΔN_2 are those of the UCLA studies cited above.

Only the exposure-chamber study of Weinmann and colleagues (1995a,b,c) has carefully investigated the relation of acute ozone exposures to changes in small airway function. To provide a more accurate measure of small airway responses, $FEF_{25\%-75\%}$ was corrected for the FVC reductions associated with ozone exposure. In addition, the ratio of $FEF_{25\%-75\%}$ to FVC was evaluated. This ratio has the units of the reciprocal of time (1/time) and can be interpreted as an indirect estimate of the reciprocal of the time constant of the lung (Tager et al. 1986). The authors observed decrements in $FEF_{25\%-75\%}$ that were always larger than those for FVC and FEV_1 but also were much more highly variable. Moreover, the $FEF_{25\%-75\%}$ decrements were significantly more likely than those for FEV_1 to persist after 24 hours (Weinmann et al. 1995c). The ratio of $FEF_{25\%-75\%}$ to FVC also was decreased, which may reflect an overall increase in the time constant of emptying the lung as a consequence of acute small airway responses (Weinmann et al. 1995c).

Given the relatively small magnitude of effect on measures of small airway physiology that is likely to be observed in population-based studies (Detels et al. 1987, 1991; Stern et al. 1989) and the greater reported between-subject variability (Knudson et al. 1976) and within-subject variability of measures of flows over the middle and terminal portions of the MEFV curve (McCarthy et al. 1975; Hutchison et al. 1981), it is essential for the purposes of study planning to have estimates of the variance of these measures that are both reliable and precise. Moreover, given the more stringent equipment and protocol demands (time, subject cooperation, and lack of portability) for the SBNW test and the uncertainty about the factors that govern ΔN_2, it is important to evaluate precisely the variability of this measure in relation to flows derived from the more easily obtained MEFV curve.

In general, subjects were better able to perform the protocol for obtaining the MEFV curves, despite the addition of the more stringent peak flow requirement, than the SBNW test protocol. At test session 1, 96% of subjects could produce at least two acceptable MEFV curves compared with 88% for SBNW curves (Table 4). At test session 2, which would correspond to a follow-up visit in an epidemiologic study, only 3 subjects (1.2%) could not produce at least two acceptable MEFV curves compared with 21 subjects (8.9%) who could not provide two measures of ΔN_2. Thus, all other issues being comparable, SBNW is likely to result in more missing data, which has implications for study efficiency and data analysis.

The mean, sex-specific within-subject CVs for volumes and flows (unadjusted for height) derived from the MEFV curves (Table 6) cannot be compared with those in any large population studies because individual CVs are not reported. However, a number of small studies provide data for comparison. Hutchison and coworkers (1981), in a study of 39 subjects aged 10 to 16 years, found average individual CVs for FVC of approximately 3% for measurements made over 4 days and over 57 days (derived from visual inspection of their Figure 1; actual values were not given). For $FEF_{25\%-75\%}$, the comparable CVs were approximately 10% to 11%. In the Hutchison study, the variability of $FEF_{75\%}$ ($\dot{V}$maxVC25 in their study) appeared to be somewhat less than for $FEF_{25\%-75\%}$, although CVs for the former are not given. Of particular note was the lack of a statistically significant correlation between ΔN_2 and either of the two flow measures (actual correlations were not given), an observation that is consistent with the weak correlations observed in this study.

In a group of healthy subjects aged 18 to 50 years studied weekly for 10 weeks, McCarthy and coworkers (1975) observed a mean CV for $FEF_{25\%-75\%}$ of approximately 12% (range 7% to 22%, derived from visual inspection of their Figure 2; no numerical data were provided). This group included those smokers whose CVs did not appear different from those of nonsmokers. Estimates for $FEF_{75\%}$ ($\dot{V}_{25}$ in McCarthy et al. 1975, Figure 2) and FEV_1 were 16% (range 10% to 30%) and 7% (range 2% to 14%), respectively. These results were similar to those obtained for subjects tested 10 times in one dav (McCarthy et al. 1975). The means and ranges are larger than those observed in the present group owing to greater heterogeneity of age and smoking history in the McCarthy data.

In a group of 15 healthy adults aged 25 to 52 years, Rozas and Goldman (1982) reported CVs that ranged from 1.1% to 7.6% for FEV_1 with a mean of 2.8% (± 1.7%). In a small study of children by Teculescu and coworkers (1987), the average differences of mean FVC measurements (from three replicates) obtained one hour and two weeks apart were 1.6% (± 1.2%) and 3.0% (± 2.4%), respectively. The two-week percentage is identical to that obtained in the present

study for a one-week interval. Burki and coworkers (1975) provided the distribution of the CVs for vital capacity obtained during replicates of the SBNW test in 22 subjects of mean age 26.4 years (± 4.4 years). The mean CV was 2.4% (± 1.5%) with a range of 0.2% to 5.9%.

Finally, Künzli and colleagues (1995), in a study of 13 healthy, nonsmoking subjects whose average age was 24 years, observed average individual CVs for FVC of 2.7% and 3.3%, in separate evaluations of technician effects and machine effects, respectively, and CVs for FEV_1 of 2.0% and 2.2%, respectively. Thus, from the crude individual data, it appears that the current protocol has produced results for parameters derived from MEFV curves that are at least as precise, and perhaps more so, than those in other studies.

The means of the distribution of the within-subject CVs for ΔN_2 (Table 6) were similar to those reported in the study of McCarthy and coworkers (1975) (mean approximately 21%), but the distribution was somewhat more spread out in the current study. Teculescu and colleagues (1987) evaluated the variability of parameters from the SBNW test in 48 children aged 10 to 16 years selected at random from a population-based epidemiologic study. Tests to obtain SBNW curves were repeated either one hour or one week after the initial test. For three consecutive, acceptable replicates for ΔN_2, individual CVs ranged from 1.1% to 27.1% with a mean (± SD) of 12.9% (± 6.3%). Individual CVs for FVC in this group had a mean of 2.2% (± 1.3%).

Mean individual CVs for ΔN_2 of approximately 23% and 25% were presented by Hutchison and coworkers (1981) for replicate tests made over 4 days and 57 days, respectively; ΔN_2 was obtained by a hand-drawn line through phase III of the SBNW curve (anchor volumes not specified). Marcq and Minette (1976) provided data from 11 nonsmokers (ages not given) who were selected because they had been trained to perform the SBNW test. Subjects were studied five times in one day and produced three replicates at each test time. The mean CV for ΔN_2 was 12.5% (± 5.5%) with a range from 4.3% to 21.4%.

Therefore, on the basis of published data, it appears that the within-subject variability tends to be greater for our sample, although it is less than that in the one study whose subjects are closest to ours in age (Hutchison et al. 1981). To some extent, the difference could be related to the choice of algorithm to measure ΔN_2. The data from that study are derived from a least-squares linear regression of smoothed data between the 750-mL and 1250-mL volume points on the SBNW curve. Both McCarthy and associates (1975) and Teculescu and associates (1987) derived ΔN_2 as the slope of the line between 70% of vital capacity and the onset of phase IV (closing volume) of the SBNW curve. Marcq and Minette (1976) derived ΔN_2 from a hand-fitted straight line through the "last two-thirds of phase III," and Hutchison and associates (1981) used a hand-drawn line without further specification. All these studies appear to have followed quality control procedures similar to those of the present study, which appear to be even more stringent. Thus, it is possible that the results we present provide a slight overestimate of an "ideal" distribution of variance.

Although subjects were screened to minimize the presence of active chronic respiratory symptoms, a number of subjects did report the presence of chronic symptoms or a history of asthma in childhood (Table 2). The presence of such a history had no effect on the distribution of variance (Table 8). Similarly, the report of common acute respiratory symptoms in the 72 hours preceding any test session (Table 3) had no effect on the distribution of variance (Table 8). Neither sex nor area of residence appeared to have a large effect on the variance components (Table 9). In terms of ethnicity, the percentage of within-subject variability was substantially greater for the "other" category, which represents a heterogeneous group in terms of race or ethnicity—a situation that would be expected to increase the percentage of between-subject variation, if it had any effect. As neither the report of symptoms (past and before-test-session) nor the sex distribution differed by ethnicity classification, there is no obvious explanation for this difference.

The overall estimates of the variance components indicate that the variance contributed by test session is negligible for a period between sessions as short as five to seven days for all measures of pulmonary function evaluated (Table 11). Only Becklake and colleagues (1975) provided an analysis that can be compared directly with these results. Thirteen subjects, who ranged in age from 24 to 63 years (nine over age 40, three of whom were active smokers), were evaluated on two occasions one week apart (three acceptable replicates per session). In their study, ΔN_2 was derived from a line "fitted by eye to the alveolar plateau after the first 25% to 30% of VC [vital capacity] had been expired." (There was no statement as to how many persons made the measurements.) Between-day (within-subject) variance represented 16.6% of the total variance of ΔN_2. By contrast, between-day variance for vital capacity (obtained during the SBNW test) represented only 1% of the total variance, which is in keeping with FVC data for this study. It is highly likely that a major portion of the difference in the estimates for between-day variance for ΔN_2 in the Becklake data is a consequence of the hand method used for calculation.

As expected, the percentage of variability due to within-subject variability for FVC and FEV_1 (Table 10) was less

than that for $FEF_{25\%-75\%}$ and $FEF_{75\%}$. In the case of $FEF_{25\%-75\%}$, the percentage was only minimally greater than that for the volume measures. Although no published data are available for direct comparison, the mean absolute values of the FVC and FEV_1 given in Table 6 are very similar to data provided for older subjects (Tweeddale et al. 1984; Enright et al. 1995). Studnicka and colleagues (1990) provided estimates of variance components for several measures derived from MEFV curves for 392 children aged 7 to 10 years. The health status of the subjects was not provided. Estimates based on five-minute repetitions showed within-subject variance components for FVC, FEV_1, $FEF_{50\%}$ (approximately related to $FEF_{25\%-75\%}$), and $FEF_{75\%}$ of 8%, 5%, 11%, and 22% (derived from reliability coefficients presented by the authors as 1 – {within-subject variation/total variation}). In the present analysis the within-subject variance component for the flow measures is considerably smaller than that found by Studnicka, a difference that could be due to better cooperation among the older subjects in this study.

In contrast to the volumes and flows from MEFV curves, the percentage variation of ΔN_2 contributed by within-subject variation was large (Table 10). The within-subject variance of 23.9% is remarkably similar to the estimate of 25.3% that can be derived from Table 3 of Becklake and associates (1975).

The discussion thus far has focused on the inherent variability of the various measures that relate to small airways. Such estimates are of obvious importance for study efficiency and its relation to sample size (see below). An equally important aspect of studies of reliability relates to their use in estimating the validity (lack of bias) of a measure when a true standard is not available (Armstrong et al. 1994). Equation 1 presents the basic model that relates the correlation of a true measure to its observed value:

$$\rho^2_{TX} = 1 - \frac{\sigma^2_E}{\sigma^2_X} = \frac{\sigma^2_T}{\sigma^2_X}, \qquad (1)$$

where ρ_{TX} is the correlation of the true measure (T) with observed (X) (which equals the validity coefficient); σ^2_T is the variance of the true value across subjects; σ^2_X is the variance of the observed value across subjects; and σ^2_E is the variance within subjects.

The correlation known as the validity coefficient is the proportion of variance of the observed measure (measure observed with error) that is explained by the true measure. By expanding this relation, the reliability of a measure can be related to its validity.

The basic assumptions of this relation (model of parallel tests [Armstrong et al. 1994]) are the following: the correlations between the true measure and within replicate errors of the observed measure are equal to zero; the variances of the errors of the replicates are equal; and the errors between replicates are uncorrelated (Armstrong et al. 1994). Under these assumptions, the validity coefficient equals the square root of the correlation between any two measures of X (for example, any two replicates of $FEF_{75\%}$):

$$\rho_{X_1 X_2} = \frac{\sigma^2_T}{\sigma^2_{X_1}} = 1 - \frac{\sigma^2_E}{\sigma^2_{X_1}} = \rho^2_{TX_1} = \rho^2_{TX_2},$$

$$\text{thus, } \rho_{TX_1} = \rho_{TX_2} = \sqrt{\rho_{X_1 X_2}}, \qquad (2)$$

where X_1 and X_2 are replicate measures. The assumption of lack of correlation of the errors (for each replicate within a subject) is probably the least tenable of the three assumptions and is the condition that leaves most uncertain the correlation between the true and measured values. In the situation of correlated errors, the correlation between replicates of a measure can be expressed as the ratio of the between-subject variance to the total variance of the measure (between-subject variance component in Table 10), and the square root of the correlation of the replicate measures represents the upper bound of the validity coefficient. However, no lower bound can be specified in this situation (Armstrong et al. 1994).

Table 13 presents estimates of the correlation of the true value of each measure of pulmonary function and the observed value. For volumes and flows, the upper bound of the estimates of this correlation is extremely high. For ΔN_2 the estimated correlation is substantially less. Therefore, even if all of the assumptions of the parallel test model could be met, the validity of any estimates of ΔN_2 in any study will always be more suspect than for flows at low lung volumes. Consequently, any inference about ozone effects on peripheral airways based on ΔN_2 not only will be less precise than that based on $FEF_{25\%-75\%}$ and $FEF_{75\%}$, but also

Table 13. Estimates of Correlation Between True and Measured Values of Pulmonary Function Measures

	Estimated Correlation Between True and Measured Value[a] $[\sqrt{\rho^2_{TX}}]$
FVC	0.980
FEV_1	0.984
$FEF_{25\%-75\%}$	0.974
$FEF_{75\%}$	0.954
ΔN_2	0.871

[a] The estimates are based on parallel test assumptions. See the text for specifications of the parallel test model and the definition of correlation.

will be subject to greater concerns about the accuracy (lack of bias) of the actual measurements. This problem with inference is magnified in longitudinal studies because the imprecision will diminish the ability to discriminate among groups with differing exposures, and the degree of potential bias may differ from survey to survey. This latter problem is not directly measurable and, therefore, compromises confidence in the inferences made. With regard to the flow measures, ρ_{TX} for $FEF_{25\%-75\%}$ is nearly identical to that for FVC and FEV_1 and only minimally different from that for $FEF_{75\%}$. Given the data of Weinmann and colleagues (1995b) in conjunction with the data cited above that relate to ozone dosimetry and ozone-induced changes in the centriacinar region of the lung, $FEF_{25\%-75\%}$ is an ideal measure for evaluating long-term effects in epidemiologic studies from the point of view of validity. This view is further enhanced when issues of sample size are taken into account.

The variability of the measures of lung function has obvious implications for sample size in epidemiologic studies (Armstrong et al. 1994). In cross-sectional studies, in which within-subject variability often is ignored, using ΔN_2 as an outcome can be expected to require larger sample sizes than using $FEF_{25\%-75\%}$ and will probably require larger samples than using $FEF_{75\%}$ (Table 12). However, if one takes into account the effects of within-subject variability (measurement error), both flow measures are clearly superior to ΔN_2, as the effective sample size needed to detect a given difference between two exposure groups is related to $\{1/\rho^2_{TX}\}$ (Armstrong et al. 1994). According to Table 13, for a comparable percentage of difference, a cross-sectional study based on ΔN_2 would require approximately 13% more subjects than one based on $FEF_{25\%-75\%}$ and 9.5% more than one based on $FEF_{75\%}$. A cross-sectional study based on $FEF_{75\%}$ would require approximately 2% more subjects than one based on $FEF_{25\%-75\%}$.

The relative disadvantages of ΔN_2 with regard to sample size are equally apparent for the planning of longitudinal studies. In the case of estimating a simple rate of change with time (slope), both within-subject and between-subject variances are required to estimate the variance of the slope. The effects in this simple case are obvious by inspection of the formula derived by Schlesselman (1973);

$$\mathrm{Var}\,(\hat{\beta}) = \left(\sigma^2_{\beta} + \frac{12 \bullet \sigma^2_e \bullet (P-1)}{D^2 \bullet P \bullet (P-1)}\right), \qquad (3)$$

where β is the estimated rate of change of lung function, σ^2_{β} is the between-subject variance, σ^2_e is the within-subject variance, D is the duration of the study, and P is the number of measurements. The substantially greater within-subject variability of ΔN_2 compared with $FEF_{25\%-75\%}$ (approximately 4.5-fold relatively greater contribution to total variance; see Table 10) or $FEF_{75\%}$ (approximately 2.5-fold relatively greater contribution to total variance; see Table 10) would have a considerable effect on the variance of the estimated rate of change, and through this on the sample size that would be required to evaluate changes over time between groups living in different ambient ozone environments.

As noted in the Introduction, the motivation for this reproducibility study relates to interest in identifying functional correlates of alterations in peripheral airways that could be related to chronic effects of ambient ozone exposure and the desirability of conducting such a study in adolescents and young adults (Bates 1993). Two studies on the effects of passive and direct exposure to tobacco smoke in children illustrate the likely problems that could be created by the low precision of measurements of ΔN_2 (and to some extent $FEF_{75\%}$) relative to flow measures in a study of adolescents. In a study of 92 children between ages 10 and 16, passive exposure was associated with a significant decrease in $FEF_{25\%-75\%}$, but not in ΔN_2 (or $FEF_{75\%}$), despite the fact that the percentages of change were similar for all measures. Moreover, only 76 (83%) of the subjects could provide valid data for ΔN_2; flow data were available for all children. A study of the functional consequences of direct exposure through personal cigarette smoking in 628 secondary school students was only minimally more efficient than $FEF_{50\%}$ in distinguishing smokers from nonsmokers (Adams et al. 1984).

CONCLUSIONS

This study has demonstrated that it is feasible to obtain flows from the middle and terminal portions of the MEFV curve that are sufficiently precise to use in epidemiologic studies of the effects of prolonged exposure to ozone on measures of lung function that reflect the physiology of peripheral airways. From the point of view of precision, $FEF_{25\%-75\%}$ appears to be the optimal measure, although it is somewhat less desirable than $FEF_{75\%}$ because it includes flows over the effort-dependent part of the FVC maneuver. Although $FEF_{75\%}$ is less precisely measured than $FEF_{25\%-75\%}$, the differences are small, and the costs in terms of efficiency in either cross-sectional or longitudinal studies should be small. Furthermore, both $FEF_{25\%-75\%}$ and $FEF_{75\%}$ can be obtained easily from the same forced expiratory maneuvers on modern, computerized spirometers. In contrast, ΔN_2 does not seem well suited for such studies. The measure is much less precise than flow measures. The SBNW test

requires more complex equipment, and subjects are less likely to be able to produce usable data. Moreover, the advantages of ΔN_2 over flows from the terminal portion of the MEFV curve have not been conclusively demonstrated (McCarthy et al. 1976; Cosio et al. 1977).

ACKNOWLEDGMENTS

The authors acknowledge the superb technical assistance of Liz Cragen, who carried out all the recruitment and testing of the subjects, and the assistance of Greg Thompson, Director, Office of Student Research, University of California, Berkeley, who provided student-related address data.

The authors especially acknowledge David Bates for his thoughtful comments and critique during all phases of this work.

REFERENCES

Adams L, Lonsdale D, Robinson M, Rawbone R, Guz A. 1984. Respiratory impairment induced by smoking in children in secondary schools. Br Med J 288:891–895.

American Thoracic Society. 1987. Standardization of spirometry—1987 update. Am Rev Respir Dis 136:1285–1298.

American Thoracic Society. 1991. Lung function testing: Selection of reference values and interpretative strategies. Am Rev Respir Dis 144:1202–1218.

Anthonisen N, Robertson P, Ross W. 1970. Gravity-dependent sequential emptying of lung regions. J Appl Physiol 28:589–595.

Armstrong B, White E, Saracci R. 1994. Principles of Exposure Measurement in Epidemiology. Oxford University Press, New York, NY.

Bates D. 1989. Ozone—myth and reality. Environ Res 50:230–237.

Bates D. 1992. Historical introduction: The evolution of understanding of the small airways. Semin Respir Med 13:63–71.

Bates D. 1993. Detection of chronic respiratory bronchiolitis in oxidant-exposed populations: Analogy to tobacco smoke exposure. Environ Health Perspect (Suppl 4) 101:217–218.

Becklake M, LeClerc M, Strobach H, Swift J. 1975. The N_2 closing volume test in population studies: Sources of variation and reproducibility. Am Rev Respir Dis 111:141–147.

Berend N, Woolcock A, Marlin G. 1980. Simple tests in the diagnosis of emphysema and airway narrowing. Chest (Suppl 2) 77:282–283.

Blair H, Greenberg S, Stevens P, Bilunos P, Couch R. 1976. Effects of rhinovirus infection on pulmonary function of healthy human volunteers. Am Rev Respir Dis 114:95–102.

Buist A, Fleet DV, Ross B. 1973. A comparison of conventional spirometric tests and the test of closing volume in an emphysema screening center. Am Rev Respir Dis 107:735–752.

Buist A, Ross B. 1973. Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. Am Rev Respir Dis 108:1078–1087.

Burki N, Barker D, Nicholson D. 1975. Variability of the closing volume measurement in normal subjects. Am Rev Respir Dis 112:209–212.

Carey V, Weiss S, Tager I, Leeder S, Speizer F. 1996. Airway responsiveness, wheeze onset and recurrent asthma episodes in young adults: The East Boston Childhood Respiratory Disease Cohort. Am J Respir Crit Care Med 153:356–361.

Collaborative Ozone Project Group. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies, Part XI, Integrative Summary. Health Effects Institute, Cambridge, MA.

Cormier YF, Belanger J. 1981. The influence of active gas exchange on the slope of phase III at rest and after exercise. Am Rev Respir Dis 123:213–216.

Cosio M, Ghezzo H, Hogg J, Corbin R, Loveland M, Dosman J, Macklem P. 1977. The relations between structural changes in small airways and pulmonary-function tests. N Engl J Med 298:1277–1281.

DeGroodt E, Quanjer P, Wise M. 1983. Influence of external resistance and minor flow variations on single breath nitrogen test and residual volume. Bull Eur Physiopathol Respir 19:267–272.

DeGroodt E, Quanjer P, Wise M. 1984. Short and long term variability of indices from the single and multiple breath nitrogen test. Bull Eur Physiopathol Respir 20:271–277.

Detels R, Rokaw S, Coulson A, Tashkin D, Sayre J, Massey F. 1979. The UCLA population studies of chronic obstructive respiratory disease: I. Methodology and comparison of lung function in areas of high and low pollution. Am J Epidemiol 109:33–58.

Detels R, Sayre J, Coulson A, Rokaw S, Massey F, Tashkin D, Wu M. 1981. The UCLA population studies of chronic obstructive respiratory disease: IV. Respiratory effect of long-term exposure to photochemical oxidants, nitrogen dioxide, and sulfates on current and never smokers. Am Rev Respir Dis 124:673–680.

Detels R, Tashkin D, Sayre J, Rokaw S, Coulson A, Massey F, Wegman D. 1987. The UCLA population studies of chronic obstructive respiratory disease. 9. Lung function changes associated with chronic exposure to photochemical oxidants; a cohort study among never smokers. Chest 92:594–603.

Detels R, Tashkin D, Sayre J, Rokaw S, Massey F, Coulson A, Wegman D. 1991. The UCLA population studies of chronic obstructive respiratory disease: X. A cohort study of changes in respiratory function associated with chronic exposure to SO_x, NO_x, and hydrocarbons. Am J Public Health 81:350–359.

Division of Lung Diseases, National Heart, Lung, and Blood Institute. 1973. Suggested Standardized Procedures for Closing Volume. National Heart, Lung, and Blood Institute, Bethesda, MD.

Dockery D, Ware J, Ferris B, Glicksberg D, Fay M, Spiro A III, Speizer F. 1985. Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six U.S. cities. Am Rev Respir Dis 131:511–520.

Ducic S, Swift J, Martin R, Macklem P. 1975. Appraisal of a new test: Between-technician variation in the measurement of closing volume. Am Rev Respir Dis 112:621–627.

Enright P, Connett J, Kanner R, Johnson L, Lee W. 1995. Spirometry in the Lung Health Study: II. Determinants of short-term intraindividual variability. Am J Respir Crit Care Med 151:406–411.

Enright P, Johnson J, Connett J, Voelker H, Buist A. 1991. Spirometry in the Lung Health Study. 1. Methods and quality control. Am Rev Respir Dis 143:125–123.

Hall W, Breese-Hall C, Speers D. 1978. Respiratory syncytial virus infection in adults: Clinical, virologic, and serial pulmonary function studies. Ann Intern Med 88:203–205.

Hazucha M, Bates D, Bromberg P. 1989. Mechanism of action of ozone on the human lung. J Appl Physiol 67:1535–1541.

Health Effects Institute. 1994. Environmental Epidemiology Planning Project. HEI Communication Number 3. Health Effects Institute, Cambridge, MA.

Hutchison A, Erben A, Lennan LM, Landau L, Phelan P. 1981. Intrasubject variability of pulmonary function testing in healthy children. Thorax 36:370–377.

Hyatt R. 1983. Expiratory flow limitation. J Appl Physiol 55:1–8.

Ingram R, Schilder D. 1966. Effect of gas compression on pulmonary pressure, flow and volume relationship. J Appl Physiol 21:1821–1826.

Keefe M, Bennett W, Dewitt P, Seal E, Strong A, Gerrity T. 1991. The effect of ozone exposure on the dispersion of inhaled aerosol boluses in healthy human subjects. Am Rev Respir Dis 144:23–30.

Kinney P, Hayes C, Butler R, Lippmann M. 1992. Pulmonary function of military academy freshmen from areas of high and low ozone levels: Preliminary results. In: Tropospheric Ozone and the Environment: II. Effects of Modeling and Control, pp. 203–218. Air and Waste Management Association, Atlanta, GA.

Knudson R, Lebowitz M, Burton A, Knudson D. 1977. The closing volume test: Evaluation of the nitrogen and bolus methods in a random population. Am Rev Respir Dis 115:423–434.

Knudson R, Lebowitz M, Holberg C, Burrows B. 1983. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983:725–734.

Knudson R, Slatin R, Lebowitz M, Burrows B. 1976. The maximal expiratory flow-volume curve: Normal standards, variability, and effects of age. Am Rev Respir Dis 113:587–600.

Krowka M, Enright P, Rodarte J, Hyatt R. 1987. Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis 136:829–833.

Künzli N, Ackermann-Liebrich U, Keller R, Perruchoud A, Schindler C. 1995. Variability of FVC and FEV_1 due to technician, team, device and subject in an eight centre study: Three quality control studies in SAPALDIA. Eur Respir J 8:371–376.

Leeder S, Swan A, Peat J, Woolcock A, Blackburn C. 1977. Maximum expiratory flow-volume curves in children: Changes with growth and individual variability. Bull Eur Physiopathol Respir 13:249–260.

Lippman M. 1989a. Effects of ozone on respiratory function and structure. Annu Rev Public Health 10:49–67.

Lippman M. 1989b. Health effects of ozone: A critical review. J Air Pollut Control Assoc 39:672–695.

Lohman T, Roche ARM, eds. 1988. Anthropometric Standardization Reference Manual. Human Kinetics Books, Champaign, IL.

Marcq M, Minette A. 1976. Diurnal variations and reproducibility of the N_2 closing volume test in healthy subjects. Bull Eur Physiopathol Respir 12:757–770.

McCarthy D, Craig C, Cherniack R. 1975. Intraindividual variability in maximal expiratory flow-volume and closing volume in asymptomatic subjects. Am Rev Respir Dis 112:407–411.

McCarthy D, Craig D, Cherniack R. 1976. Effect of modification of the smoking habit on lung function. Am Rev Respir Dis 114:103–113.

Muylem AV, Vuyst PD, Yernault J-C, Paiva M. 1992. Inert gas single-breath washout and structural alteration of respiratory bronchioles. Am Rev Respir Dis 146:1667–1672.

Nemery B, Moavero NE, Brasseur L, Stanescu D. 1981. Significance of small airway tests in middle-aged smokers. Am Rev Respir Dis 124:232–238.

Neter J, Wasserman W, Kutner M. 1985. Applied Linear Statistical Models. Richard D. Irwin, Inc., Homewood, IL.

Niewoehner D, Leinerman J, Rice D. 1974. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291:755–758.

Ostro B. 1993. Examining acute health outcomes due to ozone exposure and their subsequent relationship to chronic disease outcomes. Environ Health Perspect (Suppl 4) 101:213–216.

Paiva M, Engel L. 1987. Theoretical studies of gas mixing and ventilation distribution in the lung. Physiol Rev 67:750–796.

Petty T, Silvers G, Stanford R, Baird M, Mitchell R. 1980. Small airway pathology is related to increased closing volume and abnormal slope of phase III in excised human lungs. Am Rev Respir Dis 121:449–456.

Picken J, Niewoehner D, Chester E. 1972. Prolonged effects of viral infections of the upper respiratory tract upon small airways. Am J Med 52:738–746.

Rozas C, Goldman A. 1982. Daily spirometric variability. Arch Intern Med 142:1287–1291.

Saetta M, Finkelstein R, Cosio M. 1994. Morphological and cellular basis for airflow limitation in smokers. Eur Respir J 7:1505–1515.

SAS Institute. 1991. SAS/STAT User's Guide (Release 6.03 Edition). SAS Institute, Cary, NC.

SAS Institute. 1992. SAS Technical Report P–229 SAS/STAT Software: Changes and Enhancements. SAS Institute, Cary, NC.

Schlesselman J. 1973. Planning a longitudinal study: II. Frequency of measurement and study duration. J Chronic Dis 26:561–570.

Stern B, Jones L, Raizenne M, Burnett R, Meranger J, Franklin C. 1989. Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. Environ Res 49:20–39.

Stern B, Raizenne M, Burnett R, Jones L, Kearney J, Franklin C. 1994. Air pollution and childhood respiratory health: Exposure to sulphate and ozone in ten Canadian rural communities. Environ Res 66:125–142.

Studnicka M, Frischer T, Hesse P, Gitsch G, Neumann M. 1990. Reliability of lung function parameters in children (abstract). Am Rev Respir Dis 141:A288.

Tager I, Segal M, Speizer F, Weiss S. 1988. The natural history of forced expiratory volumes: Effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 138:837–849.

Tager I, Weiss S, Munoz A, Welty W, Speizer F. 1986. Determinants of response to eucapneic hyperventilation with cold air in a population-based study. Am Rev Respir Dis 134:502–508.

Teculescu D, Pham Q, Hannhart B, Melet J, Marchand M, Henquel J. 1987. Computerized single-breath nitrogen washout in children: Variability and reproducibility. Clin Physiol 7:247–259.

Teculescu D, Pham Q, Varona-Lopez W, Deschamps J, Marchand M, Henquel J, Manciaux M. 1986. The single-breath nitrogen test does not detect functional impairment in children with passive exposure to tobacco smoke. Bull Eur Physiopathol Respir 22:605–607.

Teculescu D, Varona-Lopez W, Bruant A, Pham Q, Locuty J, Deschamps JP, Marchand M, Henquel J. 1990. Determinants of alveolar nitrogen slope and closing volumes in healthy adolescents. Am Rev Respir Dis 142:607–615.

Tweeddale P, Merchant S, Leslie M, Alexander F, McHardy G. 1984. Short term variability in FEV_1: Relation to pretest activity, level of FEV_1, and smoking habits. Thorax 39:928–932.

U.S. Environmental Protection Agency. 1986. Air Quality Criteria for Ozone and Other Photochemical Oxidants (Vol 4). U.S. Environmental Protection Agency, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1992a. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. U.S. Environmental Protection Agency, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1992b. Summary of Selected New Information on Effects of Ozone on Health and Vegetation: Supplement to 1986 Air Quality Criteria for Ozone and Other Photochemical Oxidants. U.S. Environmental Protection Agency, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1995. Air Quality Criteria for Ozone and Related Photochemical Oxidants (Vol III). U.S. Environmental Protection Agency, Research Triangle Park, NC.

Wang X, Dockery D, Wypij D, Fay M, Ferris B. 1993a. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 15:75–88.

Wang X, Dockery D, Wypij D, Gold D, Speizer F, Ware J, Ferris B Jr. 1993b. Pulmonary function growth velocity in children 6 to 18 years of age. Am Rev Respir Dis 148:1502–1508.

Weinmann GG, Bowes SM, Gerbse MW, Kimball AW, Frank R. 1995a. Response to acute ozone exposure in healthy men: Results of a screening procedure. Am J Respir Crit Care Med 151:33–40.

Weinmann GG, Liu M, Proud D, Weidenback-Gerbase M, Hubbard W, Frank R. 1995b. Ozone exposure in humans: Inflammatory, small and peripheral airway responses. Am J Respir Crit Care Med 152:1175–1182.

Weinmann GG, Weidenbach-Gerbase M, Foster WM, Zacur H, Frank R. 1995c. Evidence for ozone-induced small-airways dysfunction: Lack of menstrual cycle and gender effects. Am J Respir Crit Care Med 152:988–996.

Wright J, Cagle P, Churg A, Colby T, Myers J. 1992. Diseases of the small airways. Am Rev Respir Dis 146:240–262.

ABOUT THE AUTHORS

Biographical sketches of each author are included at the end of Part II.

ABBREVIATIONS

ANOVA	analysis of variance
BTPS	body temperature and pressure, saturated
CV	coefficient of variation [(standard deviation/mean) × 100]
ΔN_2	slope of phase III of the single-breath nitrogen washout curve
FVC	forced vital capacity
FEV_1	forced expiratory volume in one second
$FEF_{25\%-75\%}$	forced (maximum) midexpiratory flow (between 25% and 75% of FVC)
$FEF_{50\%}$	forced expiratory (instantaneous) flow at 50% of FVC
$FEF_{75\%}$	forced expiratory (instantaneous) flow at 75% of FVC (point at which 75% of FVC has been exhaled)
LAB	Los Angeles Basin
MEFV	maximum expiratory flow-volume (curve)
PEFR	peak expiratory flow rate
PFT	pulmonary function test
ppb	parts per billion
SBNW	single-breath nitrogen washout (curve or test)
SEE	standard error of the estimate
SFBA	San Francisco Bay Area

INVESTIGATORS' REPORT

Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure

Part II: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)

Ira B. Tager, Nino Künzli, Frederick Lurmann, Long Ngo, Mark Segal, and John Balmes

ABSTRACT

An extensive body of data supports a relation between acute exposures to ambient ozone and the occurrence of various acute respiratory symptoms and changes in measures of lung function. In contrast, relatively few data are available on the human health effects that result from long-term exposure to ambient ozone. Current efforts to study long-term ozone-related health effects are limited by the methods available for ascertaining lifetime exposures to ozone.

The present feasibility study was undertaken as part of the Health Effects Institute's Environmental Epidemiology Planning Project (Health Effects Institute 1994) to (1) determine whether, in the context of an epidemiologic study, reliable estimates can be obtained for lifetime exposures to ozone by combining estimates from lifetime residential histories, typical activity patterns during life, and residence-specific ambient ozone monitoring data; (2) identify the minimum data required to produce reliable estimates of lifetime exposure; and (3) analyze the relations between various estimates of lifetime ozone exposure and measures of lung function.

A convenience sample of 175 first-year students at the University of California, Berkeley, who lived all of their lives in selected areas of California (the Los Angeles Basin or the San Francisco Bay Area), were studied on two occasions (test and retest or test sessions 1 and 2), five to seven days apart. Residential and lifestyle data were obtained from a questionnaire: residence-based ambient ozone exposure values were assigned by interpolation of ambient ozone monitoring data to residential locations. Estimated lifetime exposure was based on average ozone levels between 10 a.m. and 6 p.m. and hours of exposure to ozone concentrations greater than 60 parts per billion (ppb)*. "Effective" lifetime exposure to ozone was based on a weighted average of estimated time spent in different ambient ozone environments as determined by different combinations of activity data. Pulmonary function was evaluated with flows and volumes from maximum expiratory flow-volume curves and slope of phase III of the single-breath nitrogen washout (SBNW) curves.

Although the test-retest reliability of the residential history was acceptably high only for first and second residences, most of the unreliability for other residences came from residences occupied for relatively short durations. Therefore, the test-retest reliability of estimated lifetime exposure to ozone was high, with intraclass correlations greater than 0.90 for all approaches evaluated.

Multiple linear regression analyses showed a consistently negative relation between estimates of lifetime exposure to ozone and flows that reflect the physiology of pulmonary small airways. No relation was observed between lifetime ozone exposure and forced expiratory volume or the slope of phase III, and the relation between lifetime exposure and forced expiratory volume in one second was inconsistent. The results of the flow measures were unaffected by the method used to estimate lifetime exposure and gave effect estimates that were nearly identical.

The data from this study indicate that useful and reproducible estimates of lifetime ozone exposure can be obtained in epidemiologic studies by using a residential history. However, the total burden of ozone to which the subjects were exposed cannot be determined accurately from such data. Nonetheless, the estimates so obtained appear to be associated with alterations in pulmonary function that are consistent with the predicted site of maximum effect of ozone in the human lung.

This Investigators' Report is Part II of Health Effects Institute Research Report Number 81, which also includes *Part I: Variability of Pulmonary Function Measures*, by Dr. Ira Tager and associates; *Part III: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)*, by Dr. Patrick Kinney and associates; a Commentary by the Health Review Committee on all three Investigators' Reports; and an HEI Statement about the research projects. Correspondence concerning the Part II Investigators' Report may be addressed to Dr. Ira Tager, School of Public Health, University of California, Berkeley, CA 94720-7360.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations appears at the end of the Investigators' Report.

INTRODUCTION

Over the past several decades, an extensive body of data has been accumulated that supports a relation between short-term exposures to concentrations of ambient ozone within the range of the current U.S. air quality standards and the occurrence of various acute respiratory symptoms and changes in various measures of lung function in humans (U.S. Environmental Protection Agency 1986, 1992a, 1995).

In contrast to the situation for acute health effects, relatively few data are available with regard to health effects in humans that result from long-term exposure to ambient ozone. Increasing exposure to ambient ozone has been associated with increased occurrence of chronic obstructive pulmonary disease and asthma (Abbey et al. 1993), chronic changes in the nasal mucosa (Calderon-Garciduenas et al. 1992; Calderon-Garciduenas and Roy-Ocotla 1993), and reductions in average levels of forced expiratory volumes measured as forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) (Schwartz 1989; Stern et al. 1989, 1994), in midexpiratory flows (Kinney et al. 1992), and in performance results on tests that reflect small airway physiology (Detels et al. 1987). However, the 1995 U.S. Environmental Protection Agency (EPA) summary of the health effects attributable to ozone concluded that current data, at best, are suggestive of an association between health effects and prolonged exposure to ambient levels of ozone. Both the EPA evaluation and the report of the HEI Environmental Epidemiology Planning Project Working Group on Tropospheric Ozone (Tager 1993) indicated that one major limitation of the current efforts to study long-term ozone-related health effects concerns the methods available for ascertaining lifetime exposures to ozone.

Cross-sectional epidemiologic studies of health and long-term exposure to ambient ozone have used rather simplistic means to estimate lifetime (more correctly, "typical") ozone exposure for subjects. Generally, the subjects must be resident in the study community for some specified number of years before the actual study (Hodgkin et al. 1984; Schwartz 1989; Stern et al. 1989, 1994; Calderon-Garciduenas et al. 1992). Although longitudinal studies do provide a more detailed exposure history over the period of follow-up, they usually lack information about cohort members before the beginning of the study and do not provide estimates of the cumulative exposures that cohort members are likely to have experienced (Detels et al. 1979, 1987). Furthermore, virtually all such studies assign concentrations of ambient pollutants from monitoring networks to all individuals in entire geographic areas without any further refinement of the assignments (Detels et al. 1979; Kinney et al. 1992; Stern et al. 1994). Any refinement that is made most commonly involves the interpolation of the monitor reading to the centroid of a given area (Schwartz 1989). The amount of time that individuals spend outdoors and the nature of their activities in outdoor environments are rarely considered.

The one exception to the above comments is the Adventist Health Study (Abbey et al. 1991b, 1993). This study, more than any other epidemiologic study, attempted to assign exposures within the context of microenvironmental exposure modeling (Duan 1982; Ott 1982). This study sought to maximize the time individuals actually resided in the communities on which the exposure estimates were based by requiring that all subjects were residents for at least 11 years before the beginning of the study. In addition to a detailed set of criteria for interpolating ambient monitoring data to specific geographic residential locations, the investigators considered factors such as the time subjects spent at work, time spent outdoors, and time spent away from the study areas. These investigators reported that all of the parameter estimates for pollutant effects (ozone and total suspended particulate matter) increased when the cumulative exposure estimates were adjusted for the time that individuals typically spent indoors (Abbey et al. 1993). Ozone exposure metrics also were developed to provide (concentration × time) estimates of ozone exposure and hours spent in environments relative to specific cutoff points of ambient ozone concentrations; however, few quantitative details about the effects of adjustment on the estimates are provided. Unfortunately, this study was limited by several factors. Subjects were required to be at least 25 years of age, and a large portion of lifetime exposure could not be estimated for many older subjects. No pulmonary function data were available to test quantitatively for the presence of an exposure-response effect at ambient ozone concentrations.

Although epidemiologic studies on ozone (and other pollutants) all have focused on the levels of exposure, it is the dose received by the target organ that ultimately determines the likelihood and the extent of any health effects that can be attributed to an ambient pollutant. In this sense, exposure is an imperfect surrogate for dose. In a general context, the dose of a pollutant (e.g., ozone) that is delivered to an individual's respiratory system is a function of (1) the individual's location (the microenvironment); (2) the concentration of the pollutant in the microenvironment; (3) the time an individual spends in a given microenvironment; (4) the ventilation rate (usually specified in terms of activities in which an individual is engaged in the microenvironment); and (5) the deposition properties of the pollutant under particular ventilatory conditions (Ott 1982). Al-

though it is not feasible to measure dose directly in a large epidemiologic study, it may be feasible to measure several of the elements that affect dose. In the context of epidemiologic studies, the first four of the preceding factors, in aggregate, can be considered as elements of "effective exposure."

Given that ozone is a regional, outdoor pollutant with a rather stereotypical diurnal variation, the elements of effective exposure can be recast as three components, estimates of which may be feasible in epidemiologic studies: (1) residential location; (2) typical amount of time spent outdoors during the hours when ozone is present in the atmosphere at concentrations above "background"; and (3) outdoor activities during those hours. Residential location becomes the surrogate as well as a reference for the concentration of the pollutant in the microenvironments; therefore, its utility depends on the existence of a data base of ambient air pollution data that is historically long enough to span the lifetimes of the subjects and dense enough to permit interpolation to all residences in the study sample. To determine the typical amount of time spent outdoors, the subjects' macroenvironment is partitioned into two simple microenvironments (indoors and outdoors). Histories of typical activity patterns serve as imperfect surrogates for typical ventilatory distributions in the microenvironments.

In light of the above formulation, it would be desirable to determine the extent to which epidemiologic studies of the respiratory health effects of long-term (lifetime) exposure to ambient ozone concentrations can obtain accurate and reproducible data for the three components of effective exposure. An extensive body of data on the retrospective assessment of activity patterns of patients with cardiovascular diseases (Taylor et al. 1978; Blair 1984; Laporte et al. 1985; Blair et al. 1991; Lee et al. 1992; Ainsworth et al. 1993a,b) can be brought to bear on these issues. However, to date, little attempt has been made to apply these methods to evaluate whether effective lifetime exposure to air pollutants can be reliably estimated in epidemiologic studies. The availability of a suitably long and dense ambient ozone data base created by the pollution-monitoring activities of the California Air Resources Board (CARB) made it feasible to address this issue.

SPECIFIC AIMS

The present investigation was undertaken as part of the HEI Environmental Epidemiology Planning Project to (1) determine whether, in the context of an epidemiologic study, reliable estimates can be obtained for lifetime exposures to ozone by combining estimates from lifetime residential histories, typical activity patterns during life, and residence-specific ambient ozone monitoring data; and (2) identify the minimum data required to produce reliable estimates of lifetime exposure.

Because there is no "gold standard" against which to test the accuracy of the estimates to be derived, a third specific aim was formulated as an indirect test of the validity of the estimates: (3) to carry out a preliminary analysis of the relations between various estimates of lifetime ozone exposure and measures of lung function in college freshmen who had lived their entire lives in regions with sharply contrasting ambient ozone exposure profiles, the Los Angeles Basin and San Francisco Bay Area. Specifically, this analysis was to provide a preliminary test of the hypothesis that effects of lifetime ozone exposure should be observed in lung function measurements that reflect the physiology of small peripheral airways of the lung, the site at which ozone is thought to exert its major effect on the mammalian lung (U.S. Environmental Protection Agency 1986, 1995; Collaborative Ozone Project Group 1995).

This investigation was part of a larger feasibility study that included a detailed evaluation of the variability of measures of small airway physiology that might be suitable for use in epidemiologic studies of the respiratory health effects of long-term exposure to elevated concentrations of ambient ozone. This latter evaluation is the subject of Part I of this Research Report.

METHODS

All procedures carried out were approved by the Committee for the Protection of Human Subjects of the University of California, Berkeley, and required written informed consent from each student. All students received remuneration for participation.

DEVELOPMENT OF QUESTIONNAIRES

The goal of the questionnaires was to assign values for personal ozone exposures over the lifetimes of the study subjects, who were anticipated to be in their late teens at the time of study (see below). However, because exposure itself was of interest only in so far as it relates to the potential dose of an ambient pollutant to which the target organ or system is subjected (in this case the respiratory tract), the concept of exposure was broadened to include elements that are relevant to dose: time spent in a particular environment with a given profile of ambient air pollution, and the type and intensity of activity while in that environment. This is termed an "effective exposure" in this report. The concept of effective exposure follows directly from the

microenvironmental approach to exposure assessment (Duan 1982; Ott 1982). Thus, to estimate effective exposure over a lifetime, data were required for the locations in which individuals typically spent their time throughout their lives and the types and levels of activities in which they were engaged in those environments. As individuals could not be expected to remember details of their microenvironmental exposures (Ott 1982), the concept of location was defined in terms of a general spatial location (e.g., residence), which, in turn, was divided into indoor and outdoor components. Moreover, given that ozone predominantly is an outdoor pollutant with characteristic daily and seasonal cycles, the content of the questionnaires had to capture these aspects of the ambient ozone profile.

Most epidemiologic studies that have attempted individual exposure assignments have been based on a "time-activity" diary format (Ostro et al. 1991, 1994). Such diary formats usually are intended to capture information over very short periods of time (weeks, at most), either concurrently with a subject's activity or in the immediate past (measured in days). Less detailed exposure assignments often are attempted with questions that cover a relatively circumscribed period in the recent past (e.g., the past 12 months). Less frequently, attempts have been made to reconstruct longer periods of time in terms of location of residence, but generally not in terms of detailed patterns of activity (Abbey et al. 1991b). In short, there was no existing, previously evaluated questionnaire that could serve as a template for the questionnaires in this study, in terms of the level of detail sought with regard to activity and location over an extended period of time. Therefore, a variety of sources were used as guides to the development of the questionnaires. Each source is briefly discussed below to indicate the general content of the material that was considered and the rationale for consideration.

Source Questionnaires

Adventist Health Study The Adventist Health Study represents one of the most extensive efforts to evaluate the relation between lifetime exposure to ambient ozone and chronic health effects (Abbey et al. 1991a,b, 1993). We evaluated sections of the "Respiratory Symptoms and Residence History Questionnaire" that related to residential history and residence characteristics.

University of Southern California / California Air Resources Board Child Health Study This is a large, prospective, population-based study of the acute and chronic health effects of ambient air pollution on children who reside in selected areas of the Los Angeles Basin. The overall layout of this questionnaire was taken as the pattern for the development of our questionnaires. Specific questions that evaluated characteristics of residential neighborhoods, homes, and ventilation within homes were evaluated for use.

California Air Resources Board Study of Children's Activity Patterns and Activity Patterns of California Residents These two studies were in-depth evaluations of the activity patterns over the previous 24 hours of individuals who ranged in age from newborn through adulthood (Wiley et al. 1991a,b). These studies provided comprehensive, population-based data on the exact locations and types of activities of individuals over an entire 24-hour period. We evaluated the distribution of answers to a variety of location and activity questions. The wording and structure of the relevant questions were adopted for use in our questionnaires. The specific goal was to permit answers to questions developed for our pilot study to be referenced to the population-based estimates from the CARB study (Jenkins et al. 1992). In particular, questions were constructed with answers of "Less", "About the same", or "More than others" so that these responses could be used to assign median and quartile values derived from the CARB study for time that individuals in specific age groups spent in various activities.

Study Questionnaires

As this was a feasibility study, a larger number of questions were included in the questionnaires than could be expected to be completed reliably. The goal was to identify questions that would be useful and those that would not. The final instrument contained two questionnaires, the Eligibility Questionnaire and the Main Questionnaire (Appendix A).

Eligibility Questionnaire This brief questionnaire has a form for personal data as well as brief questions on medical, smoking, and residential history. It also includes the Residential History Form, which asks for town/city, street address, zip code, and dates for all residences since birth.

Main Questionnaire For each residence listed on the Residential History Form, a separate questionnaire was completed that contained questions referenced to the particular residence and the age range while the subject lived at that residence. Questions that related specifically to outdoor activities and home ventilation patterns were referenced to specific months of the year, particularly May through October, which are the months with the highest ozone concentrations in the study areas (California Air Resources Board Technical Support Division 1990). Before implementing the Main Questionnaire within the study protocol, we evaluated it on 10 volunteer subjects to identify problems with wording and clarity.

The Main Questionnaire is organized into the following sections:

1. *Neighborhood:* housing and street patterns.
2. *Home Characteristics:* air conditioning use, windows opened and closed, heating type.
3. *Schools Attended:* dates, location in reference to residence, presence of air conditioning.
4. *General Activity Patterns:* relative time spent outdoors, relocation in relation to residence, response to air-quality advisories.
5. *Outdoor Activities:* divided into two categories based on published values for the average rate of energy expended during each activity and expressed in terms of metabolic equivalents (1 MET = 3.5 mL of oxygen/kg/min utilization = approximate resting oxygen consumption) of various activities (Blair 1984; Ainsworth et al. 1993a). "Moderate intensity activities" were those whose rates of energy expenditure were 3 to 5 MET and "heavy intensity activities" expended 5 MET or more. A list of examples of activities in each category (Physical Activity Inventory) was provided with each questionnaire. Information was obtained on the time of year such activities were performed, the typical number of times per month, the typical duration of a session, and the typical location in relation to residence.
6. *Detailed Activity List:* In contrast to the previous section, which was based on structured questions and referenced to classes of activities, this section took the form of a diary in which subjects were asked to identify all activities performed while they lived at a particular residence, the months of the year they were performed, the number of times per month, typical duration per session, and the location relative to the residence. The format was derived from the format developed and validated as the Michigan Leisure Time Activity Questionnaire (Taylor et al. 1978).
7. *Driving:* types of vehicles and locations.
8. *Work History:* jobs working outdoors.

STUDY SUBJECTS

Selection of Sample

The selection of the subjects was motivated by the fact that one component of the study was to determine the potential size of the sampling frame for a study that would compare respiratory function of adolescents who had lived all of their lives in a high-ozone environment (selected areas in the Los Angeles Basin and Southern California [LAB]) with that of adolescents who had lived all of their lives in a low-ozone environment (selected areas in the San Francisco Bay Area [SFBA]). We defined LAB as the region between latitudes 32° and 35° and longitudes 115.5° and 120.75°, and SFBA as the region between latitudes 37° and 38.5° and longitudes 121.67° and 123°. All zip codes in these areas were extracted from the zip code data base associated with the MAPINFO software package (MapInfo Corp., Troy, NY).

The list of zip codes was submitted to the Office of Student Research of the University of California, Berkeley. The exact street addresses of all students who listed their permanent residence as within these zip codes and who matriculated in the years 1988 through 1992 were provided. The yearly number of students ranged from 1,266 to 1,540 for LAB and from 1,084 to 1,318 for SFBA.

Convenience samples of subjects were recruited between August 1993 and December 1994. Advertisements were placed in print media likely to be read by students, and notices were posted in areas frequented by students. The advertisements indicated that financial remuneration would be provided. Recruitment was carried out in a series of panels that were restricted to one region or the other. Because this was a feasibility study, no effort was made to maximize the possibility that the sample of students selected from each area would be geographically dispersed (within each region), or representative.

The pilot study called for panels of subjects to be used to evaluate the questionnaire and panels of subjects for the pulmonary function variability component (see Part I of this Research Report). The initial panels focused only on questionnaire evaluation; therefore, not all students were included in the pulmonary function protocol. Several groups of subjects were selected for participation in both parts of the study. No selection criteria were applied to these protocol assignments. Only by chance did it turn out that more subjects from SFBA participated in both protocols.

Eligibility

Inclusion criteria were evaluated through the completion of standardized questions in the Eligibility Questionnaire, including the Residential History Form (Appendix A). Initial criteria for inclusion were

1. age between 16 and 20 years;
2. lifelong nonsmoker (defined as not smoking as much as one cigarette per day for more than one year) and not smoking in the year before testing;
3. no history of asthma (this criterion was modified, see below); and
4. lifelong resident of LAB or SFBA (a large number of volunteers were immigrants of Asian or Pacific Islander descent who had come to California very early in childhood).

To facilitate the recruitment of the desired sample in the time allotted for the study, the criteria had to be relaxed in some cases. Subjects with a history of asthma were entered into the study if they reported a history of asthma or wheezing that was confined to early childhood and they had not had any symptoms or taken any medication in their teen years. In the case of residence, students were included if their first residence outside LAB or SFBA did not extend past the first year of life.

IMPLEMENTATION OF STUDY PROTOCOL

The methods and procedures of the protocol were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Subjects came to a laboratory site on the campus. They were tested and retested on two occasions within five to seven days, at approximately the same time of day. All evaluations were carried out by a single technician. The selection of the interval of five to seven days for the test-retest period was motivated largely by the study of pulmonary function test reproducibility, which required that the interval between testing be reasonably short, and by the desire to minimize the number of times that students had to return to the laboratory. We felt that participation rates would fall if students were asked to return another time at a later date to answer the questionnaire again. This imposed limitations on the test-retest interval for the questionnaire. As a compromise, we arbitrarily chose one week as the interval.

On arrival in the laboratory, students completed the Eligibility Questionnaire and the Residential History Form. The technician reviewed the forms with the student on completion, and the student's eligibility was determined at that point. If eligible, the student completed the number of forms that corresponded to the number of residences reported. All forms were self-completed in the laboratory. Students were permitted to solicit help from the technician, if needed. Pulmonary function tests were performed, by the same technician, after the completion of the questionnaires.

EVALUATION OF QUESTIONNAIRES

Creation of Lifetime Residential History

Students were asked to report the location and corresponding time period for each residence. The time period was defined by a "from" date and a "to" date. The last "to" date represented the time that the student matriculated at the University of California, Berkeley. Therefore, for any comparison of residences reported during test sessions 1 and 2, the locations reported for a given month in a subject's lifetime might differ. Such differences were defined as "unreliable months." A month was classified as "unreliable" if it was undefined in terms of location at either test session or was defined differently at test sessions 1 and 2. Accordingly, "reliable months" were defined as months for which identical locations were reported (perfect agreement) on the two test sessions. "Perfect agreement" was achieved if street name and zip code or street number were identically reported at each test session. For each subject, reliable and unreliable months were summed to provide "total lifetime," from which the proportion of months of each subject's life that were defined reliably was derived. In those cases in which the date that a residence changed was defined only by year, two different months for each test session (March and September) were arbitrarily assigned. This resulted in the default assignment of six unreliable months in a given year.

The assessment of the reliability of residential history based on months of life was motivated by the decision to assign an exposure metric to each month of life and, from this assignment, to estimate a total exposure for each residence and for the total lifetime of each subject. The decision to use a month as the unit of time was based on several considerations. A preliminary analysis demonstrated that exact dates (month, day, and year) could be provided for only 50% of "from" dates and 36% of "to" dates, but that month and year could be provided for 83% and 84% of the dates, respectively. Thus, default month assignments were required for 17% of "from" and 16% of "to" dates. Furthermore, a month was also the time metric used for assessing activity patterns.

Activity History

The analysis present herein focuses solely on the data obtained from the Outdoor Activities section of the Main Questionnaire and was based on the Physical Activity Inventory examples of activities of moderate and heavy intensity that was included with the Main Questionnaire. The Detailed Activity List, which simulated a diary format, was not analyzed because a number of subjects completed this only for the last residence in which they were living before coming to the University of California, Berkeley. The questions on which the activity history was based had the following format (question numbers as in Appendix A):

HI-0. While you were living at this residence, did you engage in any of the activities listed under "Heavy Intensity Activities" on the Physical Activity Inventory Page?

HI-2. When you engaged in one or more of these activities, what was the average number of times per month that you did these activities?

HI-3. What was the average amount of time that you spent each time you did these activities from May through October?

HI-4. For how many years did you engage in at least one of these activities while you were living at this residence?

Questions HI-2 and HI-3 were repeated with reference to the months of May through October (months with highest ozone in LAB and SFBA) of the "last 12 months prior to coming to the UC Berkeley campus." The same sequence was asked for moderate activities.

The classification of activities into moderate and heavy implicitly includes the intensity of the activity as well as its type. For example, "bicycling leisurely" was listed as moderate intensity and "bicycling hard" as heavy intensity. Quantitative presentation of activity was based on "hours per month" engaged in moderate and heavy activity. The measure was derived by multiplication of answers to questions HI-2 (number of times per month) and HI-3 (hours per session). A preliminary analysis revealed that answers to questions HI-2 (frequency) and HI-3 (duration per session) were not correlated for either moderate intensity activity (Pearson correlation $r = 0.04$) or heavy intensity activity ($r = 0.11$, $p = 0.25$). Thus, neither frequency nor duration alone could be considered a reliable measure of total activity.

Subjects who reported having been engaged in activity at a given residence are termed "doers" (Jenkins et al. 1992). Furthermore, for both moderate and heavy intensity activity, three categories of answers were defined. The first group represents "nondoers," that is, subjects answering "No" to the above question HI-0. The second group represents those individuals who were doers of the class of activity but who were unable to provide answers to the quantitative questions that were required to calculate hours per month engaged in activity; that is, question HI-2 or HI-3 or both were answered with "Don't remember." The third group represents doers who provided quantitative answers to both questions HI-2 and HI-3.

The responses to question HI-4 (number of years) were not used for detailed analysis. The question was improperly structured in that the calendar time was not determined; therefore, the longer a subject lived at a residence, the less certain was the calendar time during which the activities occurred assuming that they did not occur throughout the entire time at the residence. Furthermore, in 20% of the records, the number of years of activity reported exceeded the number of years over which the subject reported having lived at the particular residence.

ASSIGNMENT OF EXPOSURE VALUES TO RESIDENTIAL LOCATIONS

A series of monthly mean measures of ozone concentrations was derived from the CARB ambient air quality data over the years 1975 through 1992, a period that spanned the entire lifetimes of the study subjects. Averages were based on data from zip codes that corresponded to street addresses that were available for students entering the University of California, Berkeley, for the years 1988 through 1992. Two of these averages were selected for use in this study: monthly average ozone concentrations between 10 a.m. and 6 p.m. and average hours per month with an ozone concentration greater than 60 ppb. Both of these averages were selected because there were clear differences in the distributions between LAB and SFBA, and because there was a reasonable distribution of values for SFBA, the low-ozone region (Figure 1). The restriction to 10 a.m. to 6 p.m. relates to the observation that, in the areas of study, most of the ambient ozone is found between these hours. Monthly 24-hour averages also were obtained for nitrogen dioxide (NO_2) and particulate matter smaller than 10 μm (PM_{10}) (or total suspended particulate matter).

Data from monitoring stations were spatially interpolated, with the use of inverse-distance–squared weighting, to the zip code region where each study subject lived. The

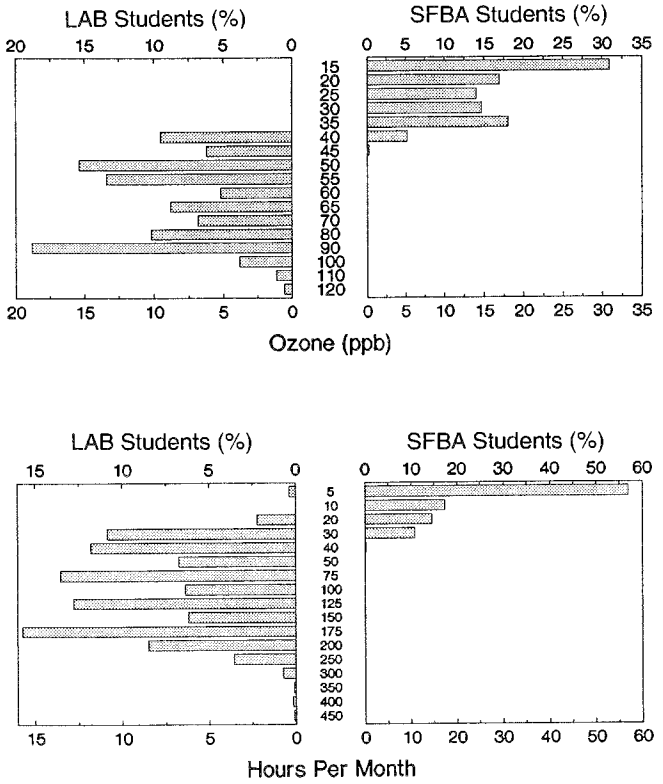


Figure 1. Distribution of monthly average ozone concentrations for University of California at Berkeley student residence zip codes from LAB and SFBA for June 15 through September 15 for the years 1988 through 1992. (Top) Monthly average ozone concentrations from 10 a.m. to 6 p.m.; (bottom) monthly average hours per month with ozone concentrations above 60 ppb.

interpolation scheme used data from three stations with valid data based on distance, nearness to roadways, and topography. Data from stations located farther than 100 km from the centroid of a zip code region were excluded. If observations were available from a station within 8 km of the centroid, then the observations from that one station were assigned to the zip code. For most of the years from 1976, the average year of birth of the study subjects, through 1992, approximately 50% of residences were within 8 km of an ozone monitoring station, about 40% were between 8 and 16 km, and about 10% were between 16 and 50 km. The situation was similar for PM_{10} and NO_2, although the percentages of residences within 8 km of a monitoring station tended to be lower than for ozone.

To explore the potential effects of uncertainties in the interpolations, the observed values at given stations were compared with values obtained by interpolation from other stations to the particular station, using the same procedures as described for the residential interpolation. For SFBA, the absolute difference between interpolated and observed ozone concentrations was less than 1 ppb and the relative difference was less than 5% for the group of stations between 8 and 16 km from the station to which interpolation was made. For the group of stations that were located between 16 and 50 km, the respective values were 2 ppb and 15%. One SD of the distribution of percentage differences was less than 20% for both groups of monitors. For LAB, the absolute and relative average differences between interpolated and observed ozone concentrations were less than 5 ppb and between 12% and 17%, respectively, for the stations located less than 8 km from the stations to which interpolation was made; less than 1 ppb and 7%, respectively, for stations located between 8 and 16 km; and less than 4 ppb and 5%, respectively, for stations located between 16 and 50 km from the station to which interpolation was made. The SDs of the percentage differences were similar to those observed for SFBA.

ASSIGNMENT OF INDIVIDUAL EFFECTIVE EXPOSURES

Realistically, there was no expectation that an assessment could be made over all of the microenvironments through which an individual passed in a lifetime, nor was there any expectation that the fine details of physical activity that took place in each of the microenvironments or categories of microenvironments could be captured with acceptable reliability. Therefore, the approach used was based on the following:

1. Residence was used as the reference for all assignments of ambient exposure.
2. Only two residence-based microenvironments were defined: outdoors and indoors. The outdoor ozone concentrations were derived as described above. The indoor concentrations were treated as a fixed fraction of the outdoor measures. If questions that related to patterns of indoor ventilation were answered reliably, these could be used to modify the fractional assignment.
3. Time spent indoors was taken as the baseline of exposure from which time spent outdoors was subtracted. This was based on the findings of the CARB activity studies, which demonstrated that, even among the most active children, the portion of a 24-hour period spent indoors is more than 85%, or 90% if enclosed transit is considered (Jenkins et al. 1992).
4. A combination of population-derived and individually derived data was required to characterize fully the effective exposure time in the time window from 10 a.m. to 6 p.m. The amount of time spent outdoors was taken as an age-dependent, fixed number of minutes per day. This ecologic assignment was based on age-group-specific quartile estimates of time spent outdoors that were derived from the CARB activity study (data available from F. Lurmann). Average time spent outdoors was calculated from a combination of this ecologic assignment and the individual activity patterns reported by the subjects.
5. The activity component of the exposure assignment reflects not only the type of activity but also its intensity. The intensity component, considered as a surrogate for ventilation, was included to capture some element of dose in the exposure assignment. Therefore, the time spent in any given activity was weighted to reflect intensity.

Ambient Ozone Concentration Component of the Exposure Assignment

The assignment of the ambient ozone metrics was as described above. For the reasons stated above, the effective exposure estimation is restricted to the monthly ozone average for the period 10 a.m. to 6 p.m. and the monthly number of hours above 60 ppb of ozone.

Time Element of the Exposure Assignment

Effective exposure time, T, spent by a subject in an ambient ozone environment included a number of components and was derived as follows: A day consisted of the eight hours between 10 a.m. and 6 p.m. to reflect the time of day when levels of ozone are most likely to be above

background. Time outdoors was assumed to occur only during these hours. Given that only two microenvironments were defined, time spent indoors was equal to eight hours minus the "baseline" time outdoors.

To reflect the fact that ozone is predominantly an outdoor pollutant, time spent indoors was weighted by a factor of 0.2. This reflects the assignment of an average indoor-to-outdoor (I/O) ozone concentration ratio of 20%. This average estimate is based on work performed by one of the investigators in Southern California that demonstrated a median I/O ozone ratio of 0.21 for LAB schools, with a tendency for the ratios to increase as outdoor ozone concentrations increase (medians = 0.16 and 0.45 for ambient ozone concentrations from 6 to 20 ppb and 60 to 110 ppb, respectively [Avol et al. 1995]). A sensitivity analysis was performed with an I/O ozone ratio of 0.5 as the weight to reflect the higher I/O ozone ratios.

In those analyses that used individual-level activity data, time outdoors was weighted to reflect the time spent in activities at the two levels of intensity defined above (3 to 5 MET and greater than 5 MET). Each hour outdoors for which activity was not reported was assigned a weight of 1. Each hour spent in moderate intensity activities (3 to 5 MET) was considered equal to two hours at baseline activity, and each hour of heavy intensity exercise was considered equal to three hours of baseline activity. These assignments were intended to reflect the increase in respiratory tract exposure (and dose) that accompanies the increased ventilation associated with increasing intensity of activity. This weighting scheme is in keeping with a scheme used for ozone dose modeling (Kleinman 1991). For example, a subject who spent an average monthly total of four hours per day outdoors, two hours of which were in moderate activity and 0.5 hour of which was in heavy activity, would be assigned an average monthly per-day "outdoor time" of $4 + 2 + (0.5)2 = 7$ hours. As the two hours spent in moderate activities and the 0.5 hour spent in heavy activities are included in the overall four hours, the effect is to assign moderate activity a weight of 2 and heavy activity a weight of 3. Thus, the total effective time can be summarized as

$$T_\ell = OUT(t)_\ell + f_{I/O}\{8 - OUT(t)_\ell\} + OUT(m)_\ell + 2\{OUT(h)_\ell\} \quad (1)$$

where T_ℓ is the ℓth month; $OUT(t)_\ell$ is the total average time per day outdoors; $f_{I/O}$ is the indoor/outdoor ratio for ozone; $OUT(m)_\ell$ is the average daily hours of moderate activity, and $OUT(h)_\ell$ is the average daily hours of heavy activity.

Monthly Effective Exposure

The effective exposure for each month at each residence was obtained as

$$EX_{ijk\ell} = OZ_{j\ell} \times T_{ijk\ell} \quad (2)$$

where $EX_{ijk\ell}$ is the effective exposure for the ith subject at the jth residence lived at during the kth age period of life during the ℓth month; $OZ_{j\ell}$ is the ozone metric during the ℓth month, at the jth residence; and $T_{ijk\ell}$ is the monthly average effective time per day outdoors for the ith subject at the jth residence lived at during the kth age period of life during the ℓth month.

In the case of the monthly eight-hour average, this effective exposure corresponds to the ppb-hours that a subject experienced, on average, every day for the entire month lived at a given residence. In the case of the monthly hours above 60 ppb, effective time outdoors was first converted to a proportion, that is, the fraction of total hours (eight) "effectively" spent outdoors. For example, the seven effective hours in the above example would be converted to 0.88 (7/8) (note that this proportion, in theory, can exceed 1). Such a subject who lived at a residence during a month in which ambient ozone concentrations exceeded 60 ppb for 40 hours would be assigned 35 "effective hours" above 60 ppb for that month.

Summary of Effective Exposure for a Given Residence

The effective exposure for a given residence was calculated as the average value across all monthly values for that residence.

$$EX_{ij} = (\Sigma\, EX_{ijk\ell}) \,/\, D_{ij} \quad (3)$$

where EX_{ij} is the effective exposure for the ith subject at the jth residence; $\Sigma\, EX_{ijk\ell}$ is the sum of monthly effective exposures as defined above, summation over ℓ months; and D_{ij} is the duration that the ith subject lived at the jth residence.

Effective Lifetime Exposure

In the final step of the exposure assignment, the overall effective lifetime (ELT) exposure for the ith subject (EX_i) was calculated as a weighted average of the residence-specific effective exposures (EX_{ij}):

$$EX_i = (\Sigma\, EX_{ij} \times D_{ij}) \,/\, (\Sigma\, D_{ij}) \quad (4)$$

where $\Sigma\, D_{ij}$ is the summation over j residences.

Approaches Used to Assign Effective Lifetime Exposures

Several different approaches, each with a different degree of complexity, were used to assign ELT exposures. The goal was to evaluate the extent to which assumptions about the various components of the exposure assignment affected the overall ELT exposure assigned to each subject. Each of these approaches used a different set of inputs into the above equations (Table 1).

Main Model (Time-Activity Model) This model (Table 2) used all of the population and individual elements for the assignment of effective exposure. For total time outdoors [$OUT(t)$], age-specific median values from the CARB study were assigned. The use of the quartile values in the older age groups was based on answers to ordinal questions in the study questionnaire. Residence-specific data were used for hours spent in activity of moderate and heavy intensity. Data for subjects younger than 6 years of age were too unreliable to be used (see Results section). Effective exposure was estimated with I/O ozone concentration ratios of 0.2 and 0.5.

Time Outdoors Model This model (Table 2) ignored individual time-activity information and used only the age-stratum-specific median values for time outdoors derived from the CARB study.

Ecologic Model The model (Table 2) derived lifetime ozone exposure solely from the residence-specific, fixed-site ambient ozone monitoring data. No time-activity data were used, nor were any assumptions made about time spent indoors versus outdoors. This approach is similar to that used in most epidemiologic studies with the exception of the requirement for lifetime residence-specific ambient air monitoring data.

Ecologic Models for Ages 12 Years and Above and Ages Below 6 Years These approaches (Table 2) are identical to the ecologic model with the exception that we used only residential data for the five to six years prior to each student's coming to the University of California, Berkeley, for the model for ages 12 and above, and only residential data for ages 1 to 5 were used for the model for ages below 6.

Table 1. Input Factors Used to Derive Effective Lifetime Exposure to Ambient Ozone

Input Factor	Unit	Derivation	Variations
Ambient outdoor ozone [OZ]	Per month over lifetime	Closest monitor(s)[a]	• Average ozone concentration 10 a.m.–6 p.m. • Monthly hours > 60ppb (10 a.m.–6 p.m.)
I/O ratio for ozone [$f_{I/O}$]	Per month over lifetime	Fixed fraction of ambient ozone	• 0.2 • 0.5
Total time spent outdoors [$OUT(t)$]	Age-stratum–specific[b]	CARB data[c]	Assigned age-stratum–specific values • Median CARB value • Quartile CARB value based on answers to ordinal question on time spent outdoors
Time spent in moderate activity [$OUT(m)$]	Per residence	Questionnaire	Hours/month for age strata 6+ years
Time spent in heavy activity [$OUT(h)$]	Per residence	Questionnaire	Hours/month for age strata 6+ years

[a] See text section Assignment of Exposure to Residential Locations for method of assignment.

[b] Age strata: birth to 2, 3 to 5, 6 to 11, 12+ years.

[c] Data are available from F. Lurmann.

PULMONARY FUNCTION DATA

The pulmonary function protocol and its evaluation are presented in detail in Part I of this Research Report and are only summarized here. All pulmonary function tests were performed on the SensorMedics 2100 System. This system uses a mass flow anemometer to measure flow of molecules (described in Appendix B). This flow measurement is independent of temperature and pressure. Flow is integrated to obtain volume. The system also provides for visual display of flow-volume curves and expiratory time during maneuvers to determine FVC. In addition, a real-time, graphic display of expiratory flow is provided that is labeled with flow rates of 300 and 600 mL/sec and used to control flow rates for the SBNW test. The volume characteristics of the instrument were calibrated twice daily with a 3-L syringe, and the nitrogen meter was calibrated at least once per day according to the manufacturer's instructions.

Maximum expiratory flow-volume (MEFV) curves were obtained with the subjects seated and using nose clips in accordance with American Thoracic Society (1991) standards. The requirement that all peak flow rates were to be within 10% of the maximum was added as another criterion (Krowka et al. 1987; see also Part I). Subjects were permitted up to eight attempts to provide three acceptable tracings. For each acceptable curve, FVC, FEV_1, maximum midexpiratory flow ($FEF_{25\%-75\%}$), and instantaneous flow at 75% of FVC, or the point at which 75% of FVC has been exhaled ($FEF_{75\%}$) were obtained by the computer.

Slope of phase III of the SBNW test (ΔN_2) was obtained after the MEFV curves. Established quality control criteria were used (Division of Lung Diseases, National Heart, Lung and Blood Institute 1973) with some modification to more closely control the expiratory flows (see Part I). Subjects were provided with a continuous visual display of their expiratory flow rates as noted above. After full expiration, subjects inhaled 100% oxygen. Exhaled nitrogen was measured continuously throughout exhalation. For a test to be acceptable, all of the following criteria had to be met:

1. after the first 500 mL of expired volume, flow between 300 and 600 mL/sec;
2. except for the first 500 mL of expiration, no expiratory flow transients above 600 mL/sec for a volume of 300 mL or more;
3. after the first 500 mL of expiration, no more than one flow transient above 600 mL/sec provided that this transient occurred over a volume of less than 300 mL;
4. no more than two flow transients below 300 mL/sec with a volume of at least 300 mL, and no more than three such transients overall;
5. expired vital capacity not less than 5% of the best FVC value obtained during the FVC maneuvers; and

Table 2. Description of Approaches Used to Assign Effective Lifetime Exposure to Ambient Ozone[a]

		Total Time Outdoors [*OUT*(*t*)] Age-Stratum–Specific Values [hours/day][b]				Activity [*OUT*(*m*) and *OUT*(*h*)]	
Approach	I/O Ratio	0–2 yr	3–5 yr	6–11 yr	12+ yr	0–5 yr	6+ yr
Main model (time-activity model)	0.2 or 0.5	0.8	2.1	0.9/2.0/3.6[c]	0.0/0.6/1.8[c]	N/A[d]	Yes
Time outdoors model	0.2	0.8	2.1	2.0	0.6	N/A[d]	—
Ecologic model	—[e]	—	—	—	—	—	—
Ecologic model age ≥ 12 yr	—	—	—	—	—	—	—
Ecologic model age < 6 yr	—	—	—	—	—	—	—

[a] All approaches used average monthly ozone concentrations for 10 a.m.–6 p.m. and the effective number of hours above an ozone concentration of 60 ppb as the ozone metrics.

[b] Based on CARB study of activity patterns (data are available from F. Lurmann).

[c] Assignment based on answer to ordinal questions on "total time outdoors"; values represent the 25th percentile/median/75th percentile of the distribution of time outdoors observed in CARB activity study for this age stratum.

[d] Report of activity too unreliable for this age group; see Results section for data.

[e] Not used for this approach.

6. no "step" changes in N_2 concentrations with continued cardiogenic oscillations.

A maximum of eight attempts were permitted to obtain three acceptable tracings. The slope of phase III was calculated by an instrument algorithm as the best fit, ordinary least-squares regression line between the 750- and 1,250-mL volume points on the SBNW curve.

DATA MANAGEMENT

All questionnaire data were entered into computer data bases through computer-based data entry screens that simulated the questionnaire layout (FSP and AF of SAS) (SAS Institute Inc. 1989a). Data entry screens included range and logic checks. Frequency distributions for responses to all questions were screened to check for outlying and inconsistent data.

STATISTICAL ANALYSIS

Analysis of Questionnaire Data

The residential and activity histories were described in terms of a series of distributional statistics and measures of repeatability for dichotomous and continuous variables (Fleiss 1981; Chinn and Burney 1987; Cicchetti and Feinstein 1990; Feinstein and Cicchetti 1990). For dichotomous variables the following statistics were obtained:

1. *Proportion of concordant pairs (A):* The proportion of "Yes-Yes" plus "No-No" responses on test-retest (Fleiss 1981).
2. *Cohen's kappa statistic:* This is a measure of agreement, adjusted for agreement that occurs by chance (Fleiss 1981). By convention, kappa values between 0.41 and 0.60 show "moderate" agreement, and those above 0.60 are considered to demonstrate "substantial" agreement (0.61 to 0.80) or "almost perfect" agreement (≥ 0.81) (Landis and Kock 1977). The kappa statistic is influenced by the overall prevalence of responses and the marginal distribution of responses (Cicchetti and Feinstein 1990; Feinstein and Cicchetti 1990). As the marginal response frequency becomes progressively imbalanced, kappa decreases even when there is very high agreement (e.g., in the extreme, "No" prevalence of 2% versus "Yes" in 98% of cases). Therefore, two other descriptive measures are provided.
3. *Positive and negative predictive values:* A positive predictive value is defined as concordant "Yes" test-retest answers as a proportion of total test-retest answers for which at least one is a "Yes." A negative predictive value has a similar derivation for answers with "No" (Cicchetti and Feinstein 1990).
4. *Estimate of sensitivity and specificity (Π):* Chinn and Burney (1987) have shown that a combined sensitivity and specificity statistic, Π, can be estimated under the assumption of equal sensitivity and specificity for "Yes" and "No" answers to questions. This assumption of equal sensitivity and specificity seemed reasonable for the data gathered in this study.
5. *Expected prevalence of a "Yes" response (P_a):* This measure provides an estimate of the true prevalence of "Yes" responses based on the data obtained from the test-retest samples (Chinn and Burney 1987). (The estimate, which is dependent on the prevalence of "Yes" responses in the sample, will be useful for sample size estimates for future studies).

Ordinal questions were evaluated with the use of log-linear models (Agresti 1990; Becker and Agresti 1992; Graham and Jackson 1993). These models permitted an evaluation of the degree to which test-retest answers agreed with regard to the ordinal ordering of the answers after adjustment for chance agreement, "linear-by-linear" or baseline agreement (tendency for test-retest answers to be high, or low, on the ordinal scale in the absence of real agreement), and agreement not due to chance or baseline agreement (true agreement). In addition, the method permitted estimation of the degree of agreement across noncontiguous portions of the ordinal scale and the extent to which agreement increased as the distance between levels of response increased. Preliminary analyses revealed that this more complex analysis resulted in inferences that were no different from those obtained with the kappa statistics cited above; therefore, the details of these analyses are not presented.

Continuous variables were evaluated in several ways:

1. *Mean of the estimates from test sessions 1 and 2 and the mean difference between test sessions:* Averages of the differences and means over all subjects and their SDs (SD_{diff} and SD_{av}, respectively) were computed. The ratio of the two SDs (SD_{diff}/SD_{av}) is a measure of reliability (Delcourt et al. 1994) and captures similar information as a plot of the difference versus the mean (Altman and Bland 1983). The smaller the ratio, the more reliable the estimate.
2. *Variance components:* A nested random effects analysis of variance (ANOVA) (PROC NESTED procedure of SAS/STAT) (SAS Institute Inc. 1989b) was used to partition the variance in the estimates into components related to differences between individuals, residences for a given individual, and test-retest reliability for a given individual.

Analyses of the Relation Between Effective Lifetime Exposure to Ozone and Pulmonary Function

The effects of ELT exposure to ozone on pulmonary function were evaluated by linear regression. The a priori hypothesis that was evaluated as the test of validity of the exposure assignment was that increasing ELT exposure to ozone would be associated with decrements in $FEF_{25\%-75\%}$ and $FEF_{75\%}$ and, to a lesser extent or not at all, in FVC and FEV_1. This hypothesis derives from the data cited above on the presumed site of ozone effect in the human lung. Despite the directionality of the hypothesis, all tests of significance and confidence intervals were based on a two-sided test to provide the most conservative approach to inference.

The pulmonary function values from the curve with the highest sum of FVC + FEV_1 were used as the dependent variables. Before being entered into the regression, each individual's ELT exposure was first standardized to permit comparison of the results between the two ozone metrics, which have different units and distributions, using

$$EX_i' = (EX_i - EX_\bullet) / SD_{EX} \quad (5)$$

where $EX_\bullet$ is the mean ELT across all EX_i and SD_{EX} is the SD of the distribution of EX_i.

The regression coefficients for EX_i' indicate the change in lung function for a change in the metric for ELT exposure to ozone equal to the SD of its distribution. The basic regression model included dummy variables for sex, region (LAB versus SFBA), and ethnicity, and also included height and a region-by-sex interaction term (based on preliminary analyses). Age was not a significant variable owing to the very narrow age range of the sample. Interaction terms for exposure and sex, region, or ethnicity were tested but were not found to be significant. All analyses fulfilled the Gaussian distribution assumptions for the residuals derived from regression models.

All analyses were carried out with SAS (SAS Institute Inc. 1989b) and STATA (Stata Corp. 1993) for personal computers.

RESULTS

GENERAL RESULTS

There were 175 subjects enrolled in the component of the overall study related to evaluating the reliability of the questionnaire (Table 3). The only significant difference between students from LAB (n = 80) and those from SFBA (n = 95) was that more subjects from SFBA were of Asian/Pacific Islander ethnicity and more subjects from LAB were of Hispanic ethnicity (Table 3). Of these 175 subjects, 130 also participated in the pulmonary function protocol (Table 4). Subjects from SFBA were significantly overrepresented (93.7% versus 51.3% for LAB; $\chi^2_{(1)} = 40.94$, $p = 0.000$) in the pulmonary function protocol, because the first panel of LAB students was used, almost exclusively, for evaluation of questionnaire reliability. There were no significant differences in the region-specific distributions of sex, ethnicity, or age between students who participated in the pulmonary function protocol and those who did not. There were no

Table 3. Characteristics of Study Subjects Who Participated in Questionnaire Reliability Study

Characteristic	San Francisco Bay Area	Los Angeles Basin	Total
Sex[a]			
Female	39 (41)	38 (48)	77 (44)
Male	56 (59)	42 (52)	98 (56)
Ethnicity[a]			
Asian/Pacific Islander	65 (68)	29 (36)	94 (54)
Caucasian	24 (25)	29 (36)	53 (30)
Other[b]	6 (7)	22 (28)	28 (16)
Age [years][c]	19.0 ± 0.6	19.1 ± 0.8	19.0 ± 0.7
Number of lifetime residences[c]	2.3 ± 1.1	2.2 ± 1.2	2.3 ± 1.1

[a] Values are number of subjects (percentage of cell total).

[b] This category includes Hispanic, African American, and "other" unspecified.

[c] Values are means ± SD.

significant differences in the mean levels of $FEF_{25\%-75\%}$ and $FEF_{75\%}$ between the 130 subjects with pulmonary function and questionnaire data and those 109 subjects who did not participate in the exposure assignment evaluation. In the group of 130 subjects ΔN_2 was slightly larger than in the group of 109 students (1.11% ΔN_2/L versus 1.02%, p = 0.07; Kruskal-Wallis ANOVA). Both FVC and FEV_1 and their sex-height^2–adjusted values were significantly larger for the 130 subjects who were included in the exposure assignment (4.37 L versus 4.04 L for FVC, p = 0.006; 3.73 L versus 3.52 L for FEV_1, p = 0.03).

One or more reported residences were excluded from the analyses for the following reasons: residence duration less than three months (one residence for 33 subjects; two residences for 5 subjects; and three foreign residences for 1 subject). These residences accounted for 4.5% of the total lifetime person-years of the study subjects. After these exclusions, there were 398 California residences that met the study criteria. Twenty-nine percent of subjects reported having only a single residence, and 16% reported having as many as four or five residences (Table 5).

Table 4. Characteristics of Study Subjects Who Participated in the Questionnaire Reliability Study and Were Selected for the Pulmonary Function Protocol

Characteristic	San Francisco Bay Area	Los Angeles Basin	Total
Sex[a]			
Female	35 (39)	18 (44)	53 (41)
Male	54 (61)	23 (56)	77 (59)
Ethnicity[a]			
Asian/Pacific Islander	60 (67)	16 (39)	76 (58)
Caucasian	23 (26)	17 (41)	40 (31)
Other[b]	6 (7)	8 (20)	14 (11)
Age [years][c]	18.5 ± 0.7	18.8 ± 1.0	18.6 ± 0.8
Height [cm][c]			
Female	162.1 ± 9.9	164.1 ± 10.9	162.7 ± 10.2
Male	174.2 ± 7.4	177.6 ± 7.0	175.2 ± 9.7
Weight [kg][c]			
Female	60.8 ± 12.9	63.2 ± 10.9	61.6 ± 12.0
Male	69.9 ± 9.7	72.5 ± 7.0	70.7 ± 9.7
Female lung function[c]			
FVC [L]	3.54 ± 0.50	3.84 ± 0.56	3.64 ± 0.54
FEV_1 [L]	3.13 ± 0.44	3.31 ± 0.41	3.19 ± 0.43
$FEF_{25\%-75\%}$ [L/sec]	3.76 ± 0.87	3.92 ± 0.87	3.81 ± 0.87
$FEF_{75\%}$ [L/sec]	2.04 ± 0.65	2.12 ± 0.68	2.06 ± 0.66
ΔN_2 [$\%\Delta N_2$/L]	0.99 ± 0.51	0.96 ± 0.37	0.98 ± 0.46
Male lung function[c]			
FVC [L]	4.87 ± 0.77	5.09 ± 0.82	4.94 ± 0.78
FEV_1 [L]	4.19 ± 0.62	4.29 ± 0.72	4.22 ± 0.65
$FEF_{25\%-75\%}$ [L/sec]	4.73 ± 1.10	4.58 ± 1.12	4.68 ± 1.10
$FEF_{75\%}$ [L/sec]	2.50 ± 0.71	2.48 ± 0.76	2.49 ± 0.72
ΔN_2 [$\%\Delta N_2$/L]	0.97 ± 0.20	0.86 ± 0.36	0.94 ± 0.41

[a] Values are number of subjects (percentage of cell total).

[b] This category includes Hispanic, African American, and "other" unspecified.

[c] Values are means ± SD.

Table 5. Distribution of Number of Lifetime Residences by Sex and Region for Subjects Who Participated in Questionnaire Reliability Study

Group	Total Number of California Lifetime Residences Reported (% of Row Total)					All Subjects[a]	All Residences[a]
	1	2	3	4	5		
Sex							
Female	19 (24.4)	30 (38.5)	15 (19.2)	8 (10.3)	6 (7.7)	78 (44.6)	186 (46.7)
Male	31 (32.0)	32 (33.0)	21 (21.7)	11 (11.3)	2 (2.1)	97 (55.4)	212 (53.3)
Raised in							
LAB	27 (33.8)	28 (35.0)	10 (12.5)	10 (12.5)	5 (6.3)	80 (45.7)	178 (44.7)
SFBA	23 (24.2)	34 (35.8)	26 (27.4)	9 (9.5)	3 (3.2)	95 (54.3)	220 (55.3)
Area total	50 (28.8)	62 (35.4)	36 (20.6)	19 (10.9)	8 (4.6)	175	398

[a] For this column the numbers in parentheses are percentages within each group.

A preliminary analysis was undertaken, with the use of responses obtained at the first session, to ascertain the extent to which students were able to provide an answer other than "Don't know/remember" for various question groups. General data that may have directly influenced the exposure assignment are summarized. Residential and activity data are presented in detail in the next two sections.

Among residence characteristics that may have influenced the exposure assignment, for 13.8% of all residences (only 0.6% of last residences), subjects could not remember if an air conditioner was present in the home. For more than 20% of all residences (exact percentage dependent on month of the year), subjects could not remember if windows were kept open or shut during various months of the year. This number was reduced to 2% or less for the last residences reported. Similar results were observed for the types of heating and cooking fuels that were used in the homes.

For more than 90% of residences, students could identify whether or not the schools that they attended were within three miles of their homes. Seventy-three percent of elementary schools and 86% of high schools were reported to be within three miles of the residences for which the report was being made. For 75% of high schools, the estimated time to travel from home to school was no more than 15 minutes (for 90%, no more than 30 minutes). This suggests that estimates of exposure based on residence also were reasonable for school locations.

All questions that were related to driving patterns and location of driving contained very high frequencies of "Don't know" (> 14%).

RELIABILITY OF RESIDENTIAL HISTORY

The number of residences and the town/city reported for each residence were identical for test and retest visits. Students who reported more than two residences were less likely to report reliably the same residential location (Table 6). Overall, for 78% of all residences test and retest addresses were identical, when an identical address was defined as report of either the same zip code and street name or the same street name and street number at both test sessions (Table 6). For approximately 8% of addresses, the street name only was inconsistently reported (data not shown), and some of these, undoubtedly, could have been assigned unequivocally to a zip code if an effort had been made to clarify the street name. If this had been done, the percentage of lifetime addresses for those with three and four residences would have increased to 85.2% and 76.3%, respectively, and the number of reliably reported first, second, and third residences would have increased to 77.3%, 90.4%, and 93.6%, respectively (from 66.3%, 83.2%, and 88.9%; see Table 6). A similar problem was identified with the "from" and "to" dates (Table 6), with reliable dates reported for only 80% or less of residences for those with three to five residences.

From the reliability of the individual residential histories, the reliability of estimated lifetime residential history was estimated. On average, each subject provided 17.8 years (± 1.2 years) of lifetime history, of which, on average, 15.8 years (± 2.6 years) was estimated reliably (Table 7). For 10% of subjects, 67% or less of their lifetime was defined reliably as determined by residential dates (Figure 2). As

expected, the reliability of total lifetime residential history was inversely related to the number of residences (Figure 2). The 50th percentiles (medians) of the percentages of reliably reported lifetimes for one, two, three, four, and five residences were 100%, 95%, 83%, 80%, and 79%, respectively—that is, for subjects with three or more residences, 50% reliably reported less than 90% of their total lifetime residential history.

Figures 3 and 4 present the impact of the unreliability of the total residence-based lifetime on ELT exposure to ozone as derived from the ecologic model (see Table 2 and Approaches Used to Assign Effective Lifetime Exposures section, above). Figure 3 shows the test-retest estimates of the average daily ozone concentration (ppb) per month (based on the eight-hour averages, see Effective Lifetime Exposure section, above) for each residence. The median per-resi-

Table 6. Percentage of Agreement in Residence Location Reporting at Test Sessions 1 and 2 and Quality of Dates

Group	Number of Students [Residences]	Identical Address (%)[a]	Number (%) Reporting at Least Month and Year[b]	
			"From" Dates	"To" Dates
Number of lifetime residences				
1	50 [50]	100	49 (98.0)	50 (100)
2	62 [124]	84.7	110 (88.7)	113 (91.1)
3	36 [108]	71.3	87 (80.6)	87 (80.6)
4	19 [76]	65.8	54 (71.1)	55 (72.4)
5		72.5	28 (70.0)	29 (72.5)
Residence number				
1 (Mostly from birth)	175	66.3	167 (95.4)	136 (77.7)
2	125	83.2	88 (70.4)	107 (85.6)
3	63	88.9	46 (73.0)	55 (87.3)
4	27	100	19 (70.4)	27 (100)
5	8	100	8 (100)	8 (100)
Total	175 [398]	78.1	328 (82.4)	333 (83.7)

[a] Identical address was defined as the same street name and zip code, or the same street name and number, reported on both visits.

[b] Starting ("from") and ending ("to") dates had to be indicated with at least a month and year; see text section Creation of Lifetime Residential History.

Table 7. Estimates of Total Lifetime Residential History Reliably Defined[a]

Total Lifetime Residences Reported	Number of Subjects	Total Time Assessed [years][b]	Total Time Defined Reliably [years][b]
1	50	17.8 ± 1.2	17.8 ± 1.2
2	62	17.4 ± 1.5	16.0 ± 2.0
3	36	17.9 ± 0.9	14.7 ± 2.7
4	19	18.0 ± 0.8	13.6 ± 2.9
5	8	17.9 ± 0.8	13.2 ± 3.3
Totals	175	17.8 ± 1.2	15.8 ± 2.6

[a] See text section Creation of Lifetime Residential History for details.

[b] Values are means ± SD.

dence difference was 0.1 ppb, and the 95th percentile of the distribution was 8.9 ppb. The overall agreement for each residence was high (intraclass correlation = 0.93), and a nested random effects ANOVA of the average daily concentration (ppb) assigned to each residence gave the following partition of the overall variance of the residence-specific estimates based on the ecologic model: between-visit variance, 6.7%; between-residence variance, 25.3%; and between-subject variance, 67.9%. Residential exposure assignments for the 23 residences with test-retest differences of more than 8 ppb tended to be of shorter duration (median = 24 months; 25th, 75th percentiles = 9.8, 56.4 months) than residences for which the differences were 8 ppb or less (median = 80 months; 25th, 75th percentiles = 38, 155 months). As the least reliable estimates of exposure assignment that are based on the ecologic model come from residences of the shortest duration, the overall lifetime estimates for each individual are likely to be estimated more reliably (see above, Equation 4). This is demonstrated in Figure 4, in which the scatter of the data around a line of identity is far less than that for the individual residence-based assignments. Only 1% of the overall variance of the ELT exposure was due to between-visit variability (i.e., intraclass correlation = 0.99) when based on the ecologic model. Ninety percent of the differences in Figure 4 were between −1.7 and 1.4 ppb.

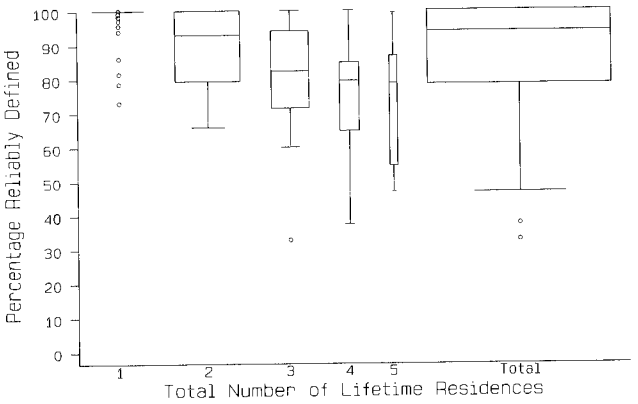


Figure 2. Percentage of total lifetime residential history defined reliably at both test sessions stratified by the number of total lifetime residences reported. Box widths are proportional to the number of subjects in each group (see Table 7). The middle bar in each box is the median, and the bottom and top ends of the box are the 25th and 75th percentiles of the distributions. Lines extending from the box have the approximate interpretation as the bounds of ± 2 SD. Circles represent data points that have the approximate interpretation of ± 3 SD.

RELIABILITY OF ACTIVITY QUESTIONS

On average, subjects reported that they performed moderate activities at 69% of residences and heavy activities at 67% (Table 8). Males were more likely to report heavy activities than were females. For both moderate and heavy activities, males reported more activity times per month and more hours per session. There were no differences in the activity patterns across ethnic groups. Inability to remember the number of times per month that an activity was performed (Table 8) was more common for activities classified as moderate (19%) than for activities classified as heavy (13%). A similar, but less distinct pattern was observed for the number of hours per session (Table 8).

Overall, residence-specific data sufficient to calculate the time individuals spent in activities were available for 77% of residences for moderate activities and 82% for

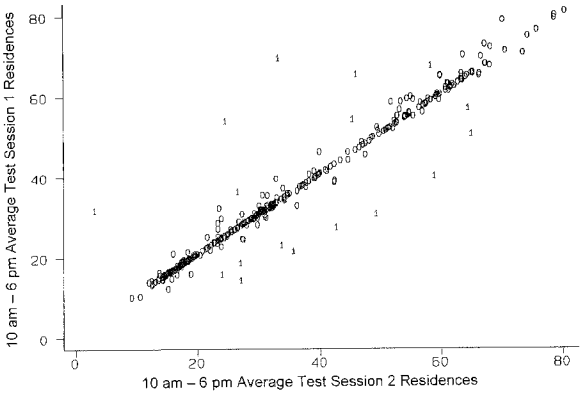


Figure 3. Estimates of average daily ozone exposure (ppb) per month for each residence, based on the ecologic model applied to eight-hour averages, from test session 1 residential history versus estimates from test session 2 residential history. The symbol 1 refers to a difference of more than 8 ppb between test sessions 1 and 2.

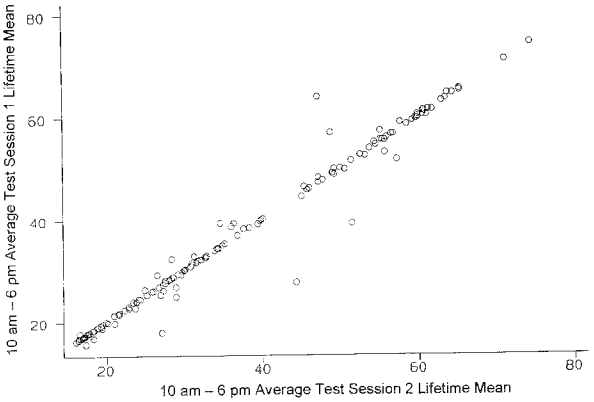


Figure 4. Estimates of each subject's lifetime, weighted-average, daily ozone exposure (ppb) per month, based on the ecologic model applied to eight-hour averages, from test session 1 residential histories versus estimates from test session 2 residential histories.

heavy activities (Table 9). There were no differences between LAB and SFBA subjects in the percentages of residences for which complete numeric data were available on doers who performed moderate and heavy activities (Table 9). Residence-specific data tended to be more complete for female than for male doers (Table 9). Students from LAB reported a higher percentage, compared with students from SFBA, of residences at which they performed moderate activities (72% versus 66%) and heavy activities (74% versus 62%) (Table 9).

The structure of the questionnaire made it difficult to determine the extent to which the completeness of the quantitative data was a function of the number of residences versus the time elapsed since the events occurred—

Table 8. Residence-Specific Distribution of Answers to Activity Questions Based on Questionnaire Responses at Test Session 1

Activity Group	Total Residences Reported	Number (%) Who Perform Activity (Doers)	Outcome of Questions About Number of Times per Month[a]			Outcome of Questions About Hours per Session[a]		
			Numeric Answer[b]	"Don't Remember"[b]	Times per Month[c]	Numeric Answer[b]	"Don't Remember"[b]	Hours per Session[c]
Moderate								
Female	183	127 (69.4)	106 (83)	21 (17)	12.8 (7.6)	111 (87)	16 (13)	1.4 (1.1)
Male	215	147 (68.4)	115 (78)	32 (22)	14.7 (9.9)	118 (80)	29 (20)	1.6 (1.1)
Subtotal	398	274 (68.8)	221 (81)	53 (19)	13.8 (8.9)	229 (84)	45 (16)	1.5 (1.1)
Heavy								
Female	183	112 (61.2)	102 (91)	10 (9)	15.1 (7.0)	98 (88)	14 (12)	1.8 (1.5)
Male	215	156 (72.6)	132 (85)	24 (15)	16.4 (9.4)	134 (86)	22 (14)	2.2 (1.0)
Subtotal	398	268 (67.3)	234 (87)	34 (13)	15.8 (8.4)	232 (87)	34 (13)	2.0 (1.3)

[a] Numeric answer = quantitative answer given; "Don't remember" = "Don't remember how much."

[b] Values are number of answers (percentage of doers).

[c] Values are means (± SD) only for doers who provided a numeric answer to the respective question.

Table 9. Completeness of Data for Doers of Moderate and Heavy Activities Based on Questionnaire Responses at Test Session 1

Activity Group	Total Residences Reported	Residences at Which Activity Was Performed	
		Total Number (%)	Percentage with Data for Times per Month and Hours per Session
Moderate			
Female	186	127 (69)	80
Male	212	147 (68)	75
LAB	178	129 (72)	74
SFBA	220	145 (66)	79
Heavy			
Female	186	112 (61)	87
Male	212	156 (73)	79
LAB	178	131 (74)	84
SFBA	220	137 (62)	81

that is, a subject who had lived at only a single residence had to recall activity over an entire lifetime, while a subject who had been living at his or her last residence for only a few years had to recall activity patterns at that residence for a relatively short period of time, without regard to the number of previous residences. The effect of average age at a residence was most striking in its effect on the completeness of the data, with data missing for most residences when the subject moved at or before 6 years of age (Table 10).

To provide a more integrated summary of the reliability of the activity questions, we created the response categories in Table 11. The classification permitted the inclusion of data for persons who did not perform a given type of activity.

The comparison of the categories "Yes" and "No" evaluates the overall repeatability of the classification into doers and nondoers. Reports for both activity groups were highly reliable, with an estimated common sensitivity and specificity of at least 93% and estimated positive and negative predictive values of at least 89% (Table 12). Estimates were very similar for LAB and SFBA subjects (data not shown).

The comparison of "Yes" + numeric answer versus "Yes" + "Don't remember" among the doers of activities evaluates the reliability of the quantitative estimates for doers. In this comparison a positive response is the ability to provide numeric answers to the quantitative questions. Based on the kappa statistic, the ability to provide a quantitative answer was only moderately reliable. However, the estimated

Table 10. Effect of Mean Age at Residence on Completeness of Data for Doers of Moderate and Heavy Activities Based on Questionnaire Responses at Test Session 1

		Residences at Which Activity Was Performed	
Activity Group[a]	Total Residences Reported	Total Number (% of Total)	Percentage Without Data for Times per Month or Hours per Session
Moderate			
Mean age ≤ 3 yr	91	17 (19)	82
Mean age > 3 to 12 yr	203	168 (83)	23
Mean age > 12 yr	104	89 (86)	11
Heavy			
Mean age ≤ 3 yr[a]	91	10 (11)	80
Mean age > 3 to 12 yr	203	161 (79)	17
Mean age > 12 yr	104	97 (93)	9

[a] Mean age indicates when subjects moved from residence.

Table 11. Response Categories to Evaluate Reliability of Activity Questions Based on Responses at Test Session 1

Category	Definition
"No" (nondoer)	Did not engage in activity
"Yes" (doer)	Did engage in activity
"Yes" + numeric answer	Engaged in activity and could provide numerical answer to questions on frequency and duration
"Yes" + "Don't remember"	Engaged in activity but could not provide numerical answer to questions on frequency or duration
Useful	Provided a consistent quantifiable answer: either a nondoer with 0 sessions per week and 0 time units per session, or a doer in the category "Yes" + numeric answer
Not useful	Doer in the category "Yes" + "Don't remember," or nondoer with entry other than 0 for questions on frequency or duration

prevalence of a positive response (Table 12) suggests that 86% or more of subjects who are doers can provide the quantitative data required to make the questions useful. The relatively low estimates for negative predictive values are largely driven by the relatively low prevalence of "Don't remember" responses and not by lack of specificity ($\Pi = 0.95$ and 0.94, for moderate and heavy activities, respectively). When the residences were stratified by age (see Table 10 for strata), data for residences at which the subjects' mean age was 3 years or less showed acceptable reliability (kappa = 0.75 ± 0.28, Π = 0.96 for hours/month) but low expected prevalence of ability to provide quantitative data (P_a = 18% for hours/month) for moderate activities. In contrast, the reliability of reported heavy activity in this age group was poor (kappa = 0.33 ± 0.26, Π = 0.38 for hours/month), with a low estimate of expected prevalence of data for hours/month (P_a = 38%; other data not shown).

Table 12. Reliability of Residence-Specific Answers to Activity Questions Based on Data from Test Sessions 1 and 2[a]

Activity Group	Total Residences Reported	Percentage of Agreement (A)	kappa ± SE	Positive Predictive Value	Negative Predictive Value	Π[b]	Expected Prevalence of a Positive Response (P_a)
Moderate							
"Yes" vs "No" answer	398	93	0.83 ± 0.05	0.95	0.89	0.96	0.71
"Yes" + numeric answer vs "Yes" + "Don't remember" (doer)	262	90	0.66 ± 0.06	0.94	0.72	0.95	0.86
Useful vs not useful	395[c]	87	0.49 ± 0.05	0.92	0.57	0.93	0.91
Heavy							
"Yes" vs "No"	398	97	0.93 ± 0.05	0.98	0.95	0.98	0.68
"Yes" + numeric answer vs "Yes" + "Don't remember" (doer)	262	89	0.56 ± 0.06	0.94	0.62	0.94	0.90
Useful vs not useful	398	90	0.48 ± 0.05	0.94	0.53	0.95	0.94

[a] See section Analysis of Questionnaire Data for definition of reliability parameters.

[b] Estimate of common sensitivity and specificity.

[c] Relevant data are missing for three residences.

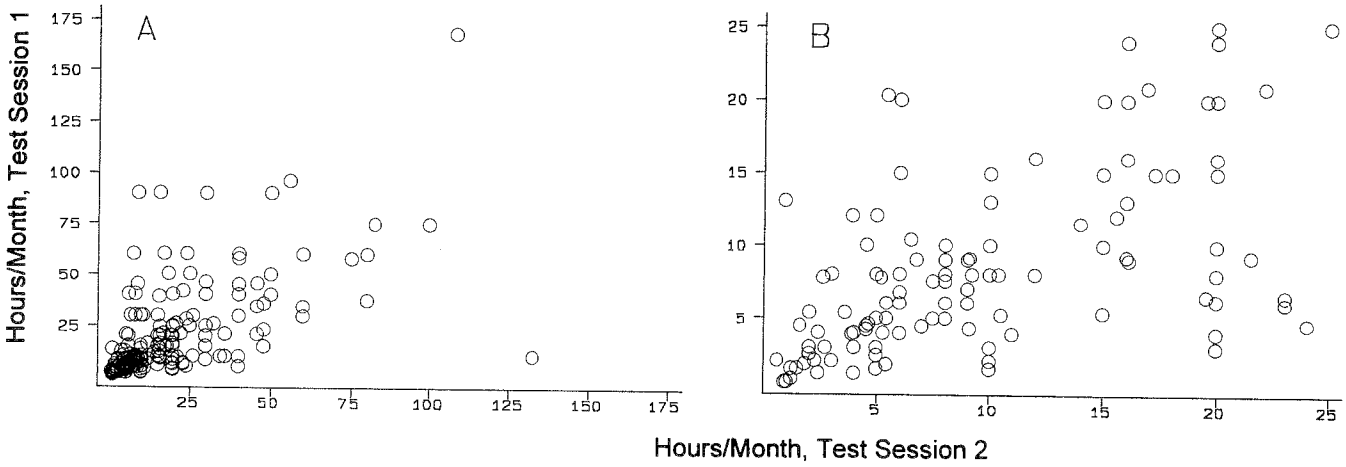


Figure 5. Comparison between test sessions 1 and 2 of estimated hours per month spent in moderate activities for doers of such activities. (A) All data presented; (B) scale expanded for those with estimates of less than 25 hours/month.

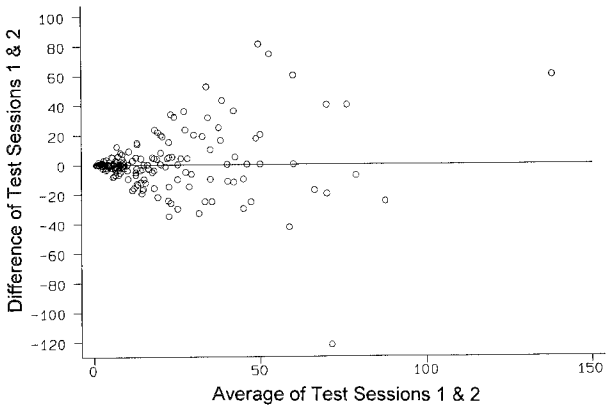


Figure 6. Differences between test sessions 1 and 2 in estimated hours spent in moderate activity versus the averages of estimates from both test sessions. Analysis is restricted to doers of moderate activities.

The above analysis ignores the fact that subjects who reliably report themselves as nondoers at a given residence do contribute quantitative data (0 times and 0 time units per session) that can be used to estimate the number of hours per month spent in the two activity groups. The comparison of "Useful" versus "Not useful" includes these subjects. In this comparison, positive agreement is defined as the provision of quantitative data at test and retest and remaining in the same category of doer or nondoer. (For this comparison, an inherently 3 × 3 table is collapsed into a 2 × 2 table.) The relatively low kappa statistics and negative predictive value for this comparison (Table 12) are largely the result of the considerable lack of balance in the margins (i.e., relatively small numbers of residences in the not useful category). The estimated prevalence of residences for which useful data can be obtained is greater than 0.90 for both activity groups, as are the estimates for common sensitivity and specificity and positive predictive value.

To evaluate the reliability of the estimates of the hours per month spent in the activity groups, the analysis was restricted to doers. Test-retest differences in estimated hours per month spent in moderate activities (for doers) are presented in Figures 5 and 6. Reliability decreased as the estimated number of hours per month increased. This is seen most clearly in Figure 6. For moderate activity, the correlations between the test-retest average and difference were 0.60 and 0.38, respectively (expectation between mean and difference is zero correlation [Altman and Bland 1983]). The average test-retest difference in the estimates was approximately one hour for both categories of activity (Table 13). The between-test session SDs for moderate activities (1.74) and heavy activities (1.89) represent 27% and 36% of the total variance for the estimated

Table 13. Reliability of Activity Measures Among Doers of Moderate and Heavy Activities

Activity Group	n[a]	Mean_{av} [b] $\pm SD_{av}$	Mean_{diff} [c] $\pm SD_{diff}$	SD_{diff}/SD_{av}	r_p[d]	Standard Deviation Between: Subject	Residence	Test	Percentage of Variance Between: Subject	Residence	Test
Moderate											
Female	95R	9.9 ± 2.8	1.0 ± 2.2	0.79	0.74	2.27	1.64	1.76	54.2	19.9	26.0
Male	105R	14.7 ± 2.5	0.9 ± 2.1	0.87	0.70	2.03	1.55	1.72	51.1	18.7	30.3
Total	200R	12.1 ± 2.7	1.0 ± 2.1	0.82	0.73	2.18	1.59	1.74	53.5	19.3	27.3
Last 12 mo[e]	114S	9.1 ± 2.6	1.0 ± 2.2	0.92	0.66	2.31	—	1.85	65.5	—	34.4
Heavy											
Female	90R	15.5 ± 2.7	1.1 ± 2.9	1.08	0.57	1.59	2.01	2.14	16.7	38.3	44.9
Male	120R	24.5 ± 2.3	1.1 ± 2.0	0.87	0.71	1.61	1.80	1.64	27.8	42.1	30.2
Total	210R	20.1 ± 2.5	1.1 ± 2.4	0.94	0.64	1.68	1.89	1.86	25.4	38.2	36.4
Last 12 mo[e]	118S	15.1 ± 2.5	1.1 ± 2.0	0.78	0.75	2.34	—	1.64	74.9	—	25.1

[a] Number of residences (R) or subjects (S).

[b] Overall mean ± SD of distribution of mean test-retest estimated hours/month in activity, log transformed.

[c] Overall mean ± SD of test-retest difference in estimated hours/month in activity.

[d] Pearson correlation coefficient for test-retest estimates.

[e] Restricted to answers that relate to the 12 months before coming to the University of California, Berkeley.

hours/month (last column of Table 13). The greater variance estimate for heavy activities was driven by females who reported these types of activities less reliably than they did moderate activities. Thus, if the variance due to residence is considered as part of the overall between-subject variance, the estimated intraclass correlations for estimates of hours/month spent in moderate and heavy activities are 0.73 and 0.64, respectively.

The ability of the subjects to report their activity patterns over shorter time intervals was evaluated by restricting the analysis to questions that asked about activities over the 12 months before the students came to the University of California, Berkeley (Table 13). There was relatively little difference in the estimates of the reliability of reporting hours per month in moderate activities (estimated intraclass correlation = 0.66). The estimated intraclass correlation for heavy activities was substantially larger (0.75), which means that between-test variability still accounted for 25% of the overall variance for the estimate of hours per month spent in heavy activities over the preceding year.

Table 14 presents reliability estimates for ELT exposure to ambient ozone for several of the approaches presented in Table 2. All ELT estimates showed very high reliability, with test-retest variability accounting for 9% or less of the total variation for any measure (i.e., intraclass correlations ≥ 91%). The estimates based on the main model for both metrics were the least reliable owing to the inclusion of the detailed activity reports in the estimates (Table 14; Figures 7 and 8). For ppb-hours based on the 10 a.m. to 6 p.m. average ozone concentrations, the main model gave the highest esti-

Table 14. Distribution of Effective Lifetime Exposure Derived from Test Session 1 and Estimates of Reliability of Effective Lifetime Exposure Based on Answers to Questions at Both Test Sessions 1 and 2

Exposure Metric	Approach[a]	I/O Ratio	Mean ± SD for Test 1	Percentile of Test Session 1 Distribution			SD_{diff}	SD_{av}	Intraclass Correlation
				25th	50th	75th			
8-Hour average [ppb-hours]	Main model	0.2	171 ± 100	92	152	226	41.3	92.4	0.91
		0.5	238 ± 123	137	209	327	43.2	117.2	0.94
	Time outdoors model	0.2	95 ± 45	54	83	137	6.8	44.1	0.99
		0.5	166 ± 77	93	144	240	11.4	76.0	0.99
	Ecologic model	—[b]	35 ± 16	20	31	51	2.41	16.2	0.99
Hours/month > 60 ppb	Main model	0.2	19.2 ± 22	1.5	8.5	35.5	6.6	21.0	0.95
		0.5	26.8 ± 29.5	2.0	10.7	53.5	7.0	28.7	0.97
	Time outdoors model	0.2	10.7 ± 11.7	0.8	4.8	23.7	1.2	11.6	0.99
		0.5	19.0 ± 20.2	1.4	8.2	41.2	2.0	20.1	0.99
	Ecologic model	—[b]	32.3 ± 34.5	2.5	13.8	70.2	3.4	34.4	0.99

[a] See Table 2 for details.

[b] Not used in ecologic model.

mates, followed by the time outdoors model and the ecologic model (Table 14). For hours of exposure above 60 ppb ozone, the ecologic model resulted in the highest average lifetime exposure, as it fails to account for time spent indoors; the time outdoors model provided the lowest estimate, and the main model, which uses all of the activity data, produced an estimate that was between those of the two other approaches.

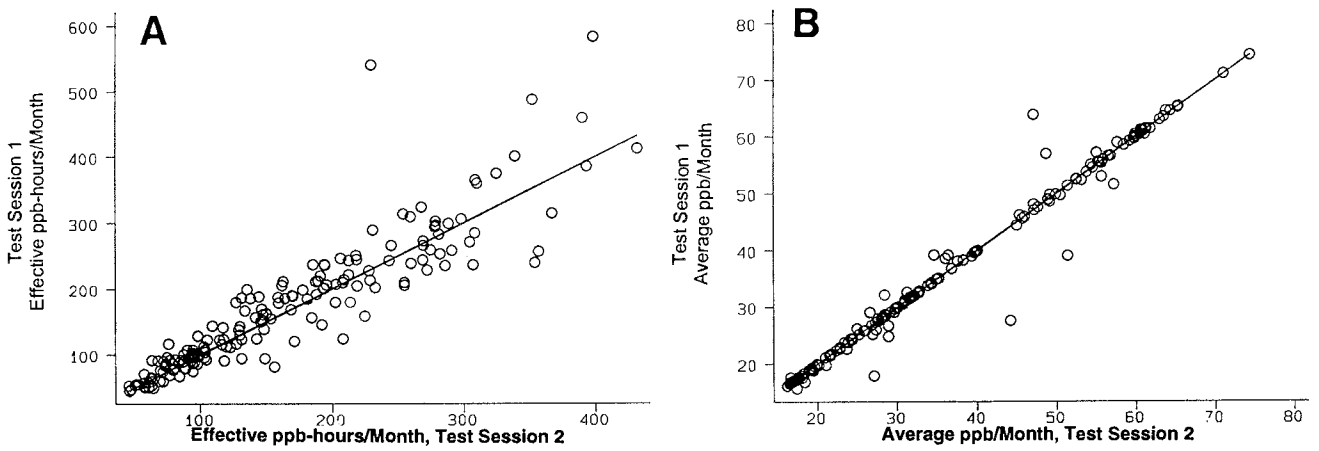


Figure 7. Differences between test sessions 1 and 2 in ozone metrics based on 10 a.m. to 6 p.m. averages. (A) "Effective" ppb-hours/month based on the main model; (B) average ppb/month based on the ecologic model.

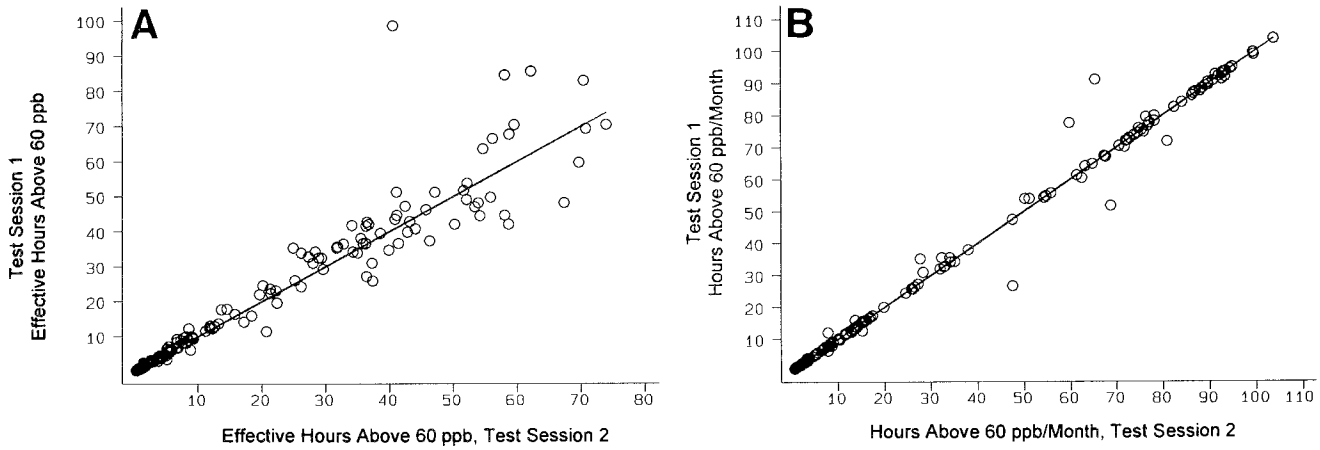


Figure 8. Differences between test sessions 1 and 2 in ozone metrics based upon hours above 60 ppb. (A) "Effective" hours above 60 ppb based on the main model; (B) average hours above 60 ppb based on the ecologic model.

The distributions of ELT exposure to ozone, based on the hours above 60 ppb as estimated in the main model, were substantially different for SFBA and LAB with little overlap (Figure 9). A similar result was observed when exposure assignment was based on the ecologic model, although there was somewhat less overlap at the low end of the LAB distribution (Figure 10). A similar pattern was observed for ppb-hours based on the 10 a.m. to 6 p.m. average ozone concentration (Figures 11 and 12). These differences are further summarized in Figure 13 for metrics based on the eight-hour average ozone concentration.

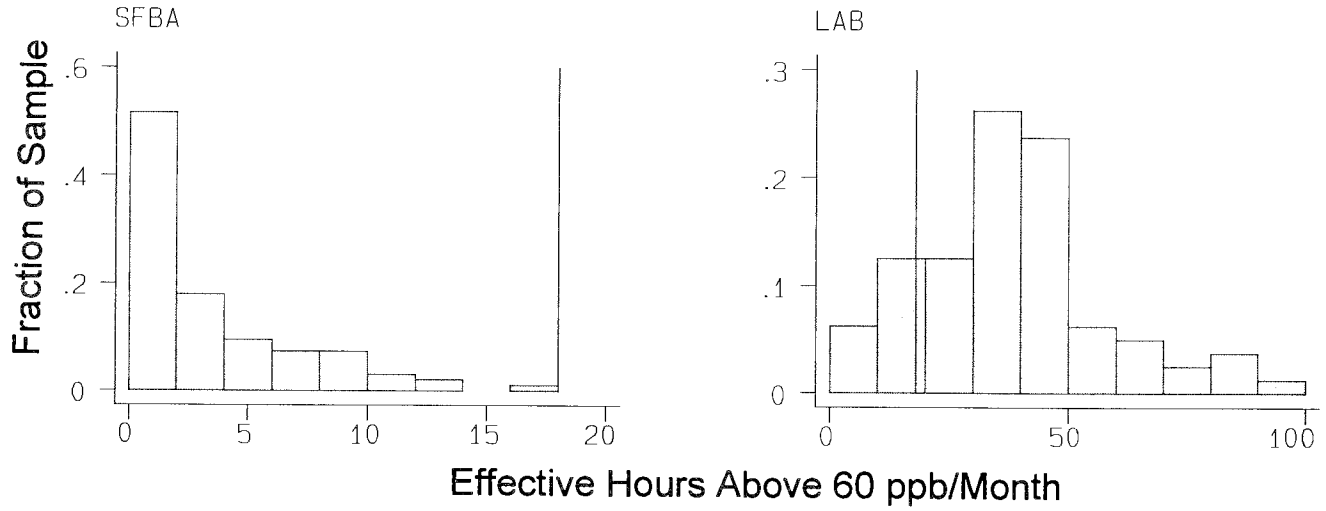


Figure 9. Distribution of estimated lifetime ozone exposure for hours above 60 ppb from the main model (I/O = 0.2) for SFBA students and LAB students. Median (25th, 75th percentiles) of distributions: SFBA, 1.8 hours (0.6, 9.0); LAB, 36.6 hours (24.5, 47.3). Vertical line = 18 hours.

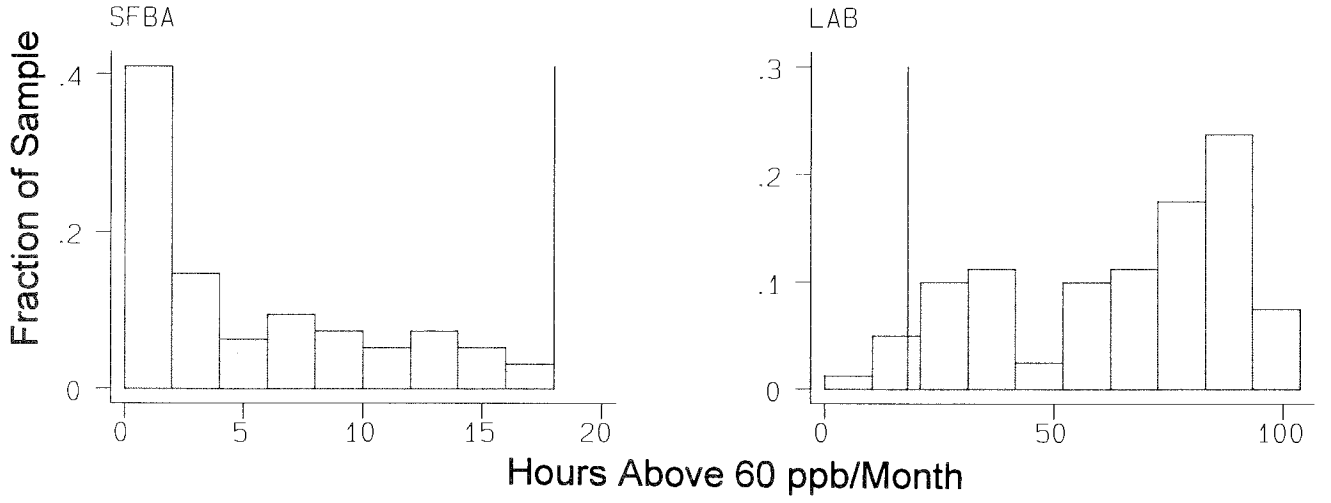


Figure 10. Distribution of estimated lifetime ozone exposure for hours above 60 ppb from the ecologic model for SFBA students and LAB students. Median (25th, 75th percentiles) of distributions: SFBA, 3.1 hours (1.1, 9.0); LAB, 72.2 hours (35.5, 88.0). Vertical line = 18 hours.

As no direct assessment of personal lifetime exposure to any ambient air pollutant is available (or likely under the assumption that no biological dosimeter is identified), no direct test of the validity of the reported activity data is possible. Therefore, the potential usefulness of the various approaches to lifetime exposure assignment (Table 2) was evaluated by an analysis of the relation between the lifetime exposure assignments under each scenario in Table 2 and the level of various measures of lung function in the subset of 130 subjects for whom lung function data were available.

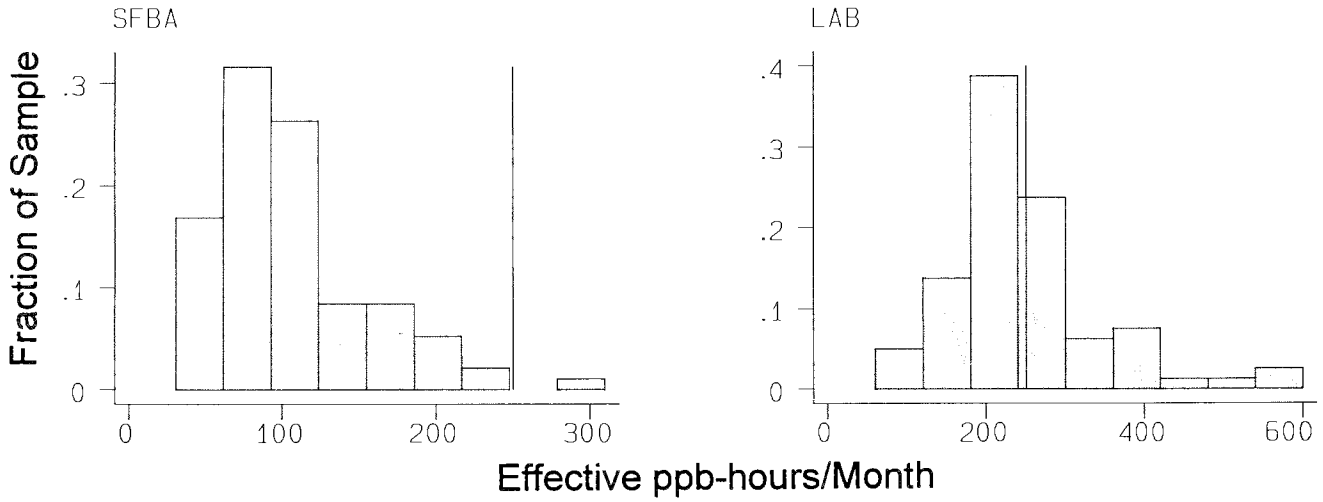


Figure 11. Distribution of estimated lifetime ozone exposure for effective ppb-hours per month derived from the main model, based on 10 a.m. to 6 p.m. average ozone concentrations for SFBA students and LAB students. Median (25th, 75th percentiles) of distributions: SFBA, 94 (77, 124); LAB, 232 (190, 370). Vertical line = 250 ppb-hours.

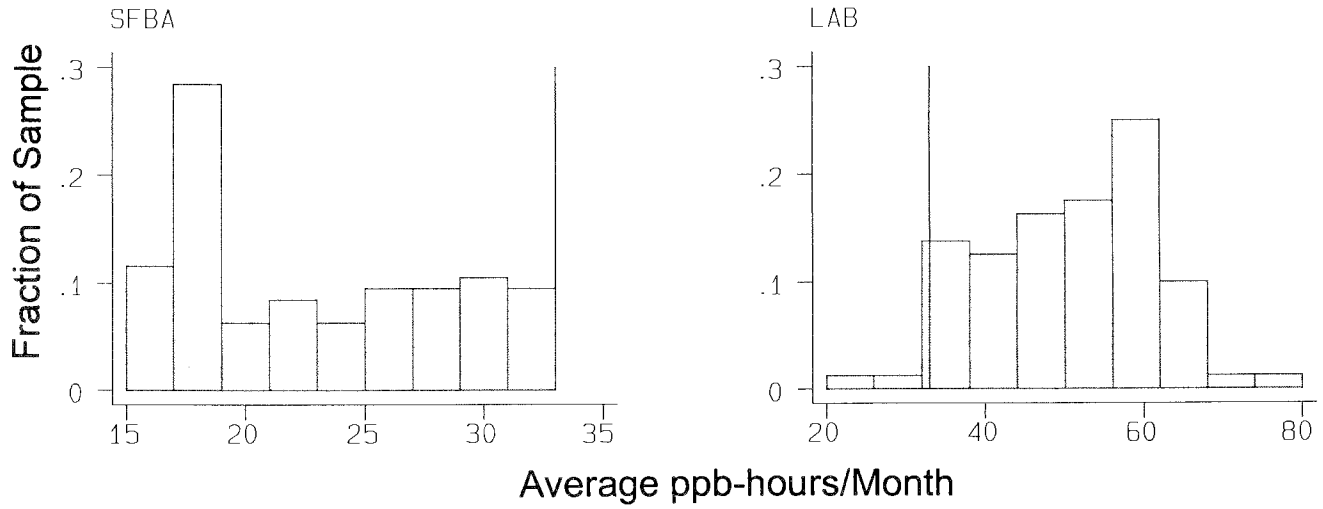


Figure 12. Distribution of estimated lifetime ozone exposure for ppb-hours per month derived from the ecologic model based on 10 a.m. to 6 p.m. average ozone concentrations for SFBA students and LAB students. Median (25th, 75th percentiles) of distributions: SFBA, 21.7 (17.4, 28.1); LAB, 52.5 (39.4, 60.2). Vertical line = 33 average ppb/month.

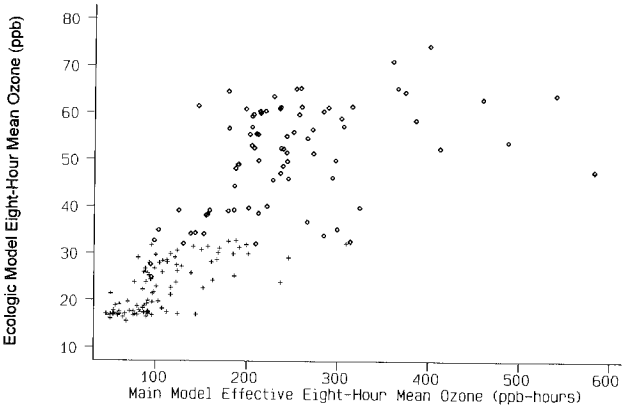


Figure 13. Effective lifetime exposure for ozone based on 10 a.m. to 6 p.m. average ozone concentrations for all 175 subjects. The *y*-axis is based on the ecologic model and the *x*-axis on the main model; + = SFBA students, Δ = LAB students.

Table 15 presents, for the 130 subjects with lung function measurements, the relevant components of several of the approaches outlined in Table 2. The estimates of effective exposure time were not significantly different for SFBA and LAB subjects. Not surprisingly, assumptions with regard to the I/O ozone exposure ratio had a strong impact on the magnitude of the effective exposure time estimates. In the main model, approximately 40% of the effective exposure time was accounted for by the weights assigned to moderate and heavy activity (average weights of 4.5 and 2.7 hours, respectively).

As expected, all estimates for ELT exposure to ozone were substantially greater for LAB subjects than for SFBA subjects (Table 15). The ELT exposures to ozone based on average ppb-hours were always the lowest for the ecologic method. However, estimates for hours above 60 ppb were greater for the ecologic method, because this measure makes no allowance for time spent indoors. As was the case for the data from all 175 subjects, there was relatively little

Table 15. Distribution of Effective Lifetime Exposure Ozone Time and Concentration

	Approach[a]	I/O Ratio	San Francisco Bay Area[b]	Los Angeles Basin[b]
Effective exposure time [hours/day]	Main model	0.2	4.5 [3.5–5.3]	4.6 [3.9–5.5]
	Main model	0.5	6.3 [5.5–7.2]	6.4 [5.8–7.3]
	Time outdoors model	0.2	2.7 [2.6–2.7]	2.7 [2.6–2.7]
Effective exposure concentration [ppb-hours][c]	Main model	0.2	94 [77–124]	228 [205–272]
	Main model	0.5	142 [111–176]	328 [291–368]
	Time outdoors model	0.2	60 [47–75]	138 [108–159]
	Ecologic model	—[d]	23 [17–28]	52 [40–60]
Effective exposure concentration [hours > 60 ppb]	Main model	0.2	2.1 [0.7–4.8]	36 [27–44]
	Main model	0.5	3.0 [0.8–7.6]	54 [38–62]
	Time outdoors model	0.2	1.1 [0.4–3.1]	24 [17–29]
	Ecologic model	—	3.2 [1.1–9.0]	70 [52–87]
PM_{10} [$\mu g/m^3$][e]	Ecologic model	—	31.2 [30–32]	51.1 [46–54]
NO_2 [$\mu g/m^3$]	Ecologic model	—	25.0 [23–26]	45.4 [41–48]
Temperature [°F]	Ecologic model	—	57.8 [57–59]	63.3 [63–64]
Relative humidity [%]	Ecologic model	—	73.2 [68–74]	68.5 [67–70]

[a] See Table 2 for definitions.

[b] Median with [25th–75th percentiles of distribution] given in brackets.

[c] Based on 10 a.m.–6 p.m. average monthly day; see text sections Time Element of the Exposure Assignment, Monthly Effective Exposure, Summary of Effective Exposure for a Given Residence, and Effective Lifetime Exposure for details.

[d] Not used in ecologic model.

[e] Uses same ecologic approach applied to ozone.

overlap in the distributions of lifetime ozone exposures for SFBA and LAB subjects. The 95th percentile for SFBA subjects' average lifetime 10 a.m. to 6 p.m. ozone exposure based on the ecologic model (32 ppb) corresponded to the 5th percentile of the distribution for LAB subjects. A similar situation was observed for the ELT exposure to ozone based on the main model (Figure 14). The correlation of the estimates of the ELT exposure to ozone based on the main model with the lifetime average derived from the purely ecologic model was 0.88 overall, 0.75 for SFBA, and 0.56 for LAB. Virtually identical relations were observed when the region-specific data were plotted for all 175 subjects and when the data were plotted stratified by those with pulmonary function data (n = 130) and those without pulmonary function data (n = 45).

Median PM_{10} and NO_2 were greater for LAB subjects (51.1 $\mu g/m^3$ and 45.4 $\mu g/m^3$, respectively) than for SFBA subjects (31.2 $\mu g/m^3$ and 25.0 $\mu g/m^3$, respectively) (Table 15), and there was relatively little overlap in the ranges.

The relations between levels of FVC and FEV_1 and estimates of lifetime ozone exposure were inconsistent, and none approached statistical significance (Table 16). For the main model, the ozone coefficients were very close to zero, and one had a positive sign. None of the coefficients for FVC was significant (Table 16). For FEV_1, the most negative

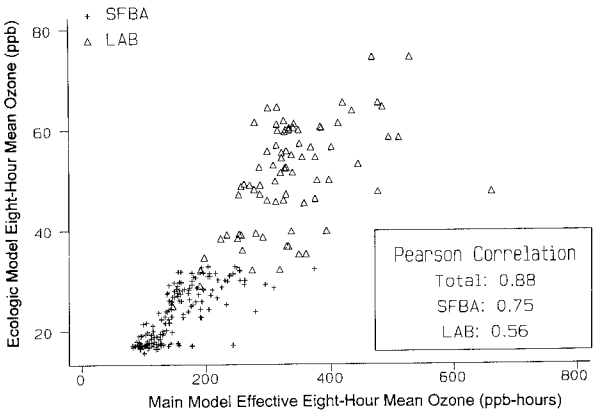


Figure 14. Effective lifetime exposure based on 10 a.m. to 6 p.m. average ozone for 130 subjects with lung function measurements. The y-axis is based on the ecologic model and the x-axis on the main model; + = SFBA, Δ = LAB.

Table 16. Relation Between Levels of Measures of Lung Function and Standardized Measures of Estimated Lifetime Exposure to Ozone

Effective Lifetime Exposure	1SD of Exposure Distribution [min/max][a]	Regression Coefficients ± SE for Ozone Effect[b]				
		FVC	FEV_1	$FEF_{25\%-75\%}$	$FEF_{75\%}$	ΔN_2
Hours > 60 ppb [hours/month]						
Main model[c]	18.8 [2/85]	0.0 ± .1	−.092 ±.085	−.326 ±.168[d]	−.252 ± .117[e]	+.033 ± .075
Time outdoors model	10.5 [2/35]	−.167 ±.111	−.195 ±.096[e]	−.361 ±.192[d]	−.242 ± .134[d]	+.017 ± .086
Ecologic model	30.8 [1/104]	−.148 ±.112	−.179 ±.096[d]	−.348 ±.193[d]	−.241 ± .134[d]	+.008 ± .086
Ecologic model: age ≥ 12 yr	28.3 [.2/110]	+.004 ± .090	−.048 ±.080	−.196 ±.156	−.190 ± .108[d]	−.045 ± .067
Ecologic model: age < 6 yr	4.3 [1/14]	−.137 ±.116	−.196 ±.099[e]	−.416 ±.200[e]	−.262 ± .139[d]	+.060 ± .080
10 a.m.–6 p.m. ppb-hours/day						
Main model[c]	89.6 [45/583]	+.066 ± .074	−.030 ±.065	−.224 ±.128[d]	−.190 ± .089[e]	−.052 ± .056
Time outdoors model	40.8 [40/199]	−.039 ±.102	−.105 ±.087	−.320 ±.174[d]	−.243 ± .121[e]	−.079 ± .079
Ecologic model	14.8 [16/74]	−.020 ±.103	−.092 ±.089	−.331 ±.176[e]	−.247 ± .122[e]	−.089 ± .079
Ecologic model: age ≥ 12 yr	12.7 [17/74]	+.109 ± .090	+.003 ± .080	−.236 ±.153	−.253 ± .105[e]	−.100 ± .067
Ecologic model: age < 6 yr	18.1 [14/75]	−.024 ±.105	−.115 ±.091	−.360 ±.180[d]	−.260 ± .125[e]	−.150 ± .080

[a] See text section Analyses of the Relation of Effective Lifetime Exposure to Ozone and Pulmonary Function for standardization [minimum and maximum ozone exposures from the distributions].

[b] For each approach, test session 1 data were used for multiple linear regression model of the form: lung function = $a + b$ (standardized lifetime ozone exposure) + c (height) + e (sex) + f (region) + g (sex × region) + error.

[c] See Table 2 for definitions of models.

[d] $p \leq 0.1$ for regression coefficient "b."

[e] $p \leq 0.05$ for regression coefficient "b."

coefficients were observed for the time outdoors model, overall ecologic model, and the ecologic model for ages 6 and below for hours above 60 ppb. An increase in lifetime hours above 60 ppb of 1 SD was estimated to result in a reduction of FEV_1 of −195 mL (95% confidence interval [CI] −7 mL, −383 mL) for the time outdoors model and −179 mL (95% CI +9 mL, −367 mL) for the ecologic model.

In contrast, levels of $FEF_{25\%-75\%}$ and $FEF_{75\%}$ consistently decreased as ELT ozone exposure increased for hours above 60 ppb and ppb-hours/day (Table 16). For hours above 60 ppb, the coefficients were relatively similar for each flow measure for the main, time outdoors, and ecologic models. Based on the main model, an increase of 1 SD in the estimated lifetime hours above 60 ppb was associated with decreases of −326 mL/sec (95% CI +3 mL/sec, −655 mL/sec) for $FEF_{25\%-75\%}$, and −252 mL/sec (95% CI −23 mL/sec, −481 mL/sec) for $FEF_{75\%}$. These average decreases represent decrements of 7% and 10% when referenced to the overall means for these flows (Table 4). The magnitude of the effect for the main model estimate for ppb-hours/day was less for both flow measures and represented decrements of 5% and 8% compared with the population means.

No meaningful relations were observed between ozone exposure estimates and ΔN_2. In fact, for ppb-hours, all of the coefficients had negative signs, which indicates decreases in the slope with increasing ozone exposure, rather than the expected increase.

Analyses were conducted to determine if the age stratum over which exposure occurred altered the relation between ELT exposure to ozone and measures of pulmonary function (Table 16). Only ecologic models were used for this analysis. Exposure was divided into that which occurred before 6 years of age and that which occurred at 12 years of age or older. For FVC and FEV_1, the estimated regression coefficients had positive signs (effect estimate in the opposite direction of expected) for both ozone metrics for exposures at 12 years or older (Table 16). For exposures before age 6, the effect on FVC was inconsistent. FEV_1 appeared to decrease with increasing hours above 60 ppb (−196 mL SD; 95% CI +390 mL, −2 mL). In contrast to the volume measures, both flow measures showed a more consistent decrease with increasing estimated ozone exposure for both ozone metrics, with the effects being largest for exposures before age 6 (Table 16). For example, for hours above 60 ppb, an increase of 1 SD in ELT exposure before age 6 was associated with a decrease in $FEF_{75\%}$ of −262 mL/sec (95% CI +10 mL/sec, −534 mL/sec) compared with a decrease of −190 mL/sec (95% CI +22 mL/sec, −402 mL/sec) for exposure that occurred at age 12 or older.

The basic regression diagnostics to evaluate the appropriateness of a linear model for describing the data are provided in Appendix D. The fit of the models was substantially better for FVC and FEV_1 than it was for $FEF_{25\%-75\%}$ and $FEF_{75\%}$ (see also Table 17, r^2). However, in the case of these flow measures, plots of the observed values versus the standardized exposure metric and plots of the residuals indicated that a linear model was a reasonable explanatory model.

A further analysis was undertaken to evaluate the extent to which it was reasonable to apply a common slope across the disparate exposure distributions for LAB and SFBA subjects (analogous to upper left-hand plots in Appendix D). Figure 15 shows the $FEF_{75\%}$ residuals from a regression of $FEF_{75\%}$ on age, height, sex, and region (exposure metric omitted) plotted against the effective lifetime ppb-hours based on the main model. The relatively horizontal, LOESS smooth curve (Stata Corp. 1993), with a typical value of 0, does not provide much evidence for the existence of separate slopes across regions, at least for these data.

Several analyses were undertaken to evaluate the sensitivity of the observations in Table 16 to various features of the main model for FEV_1 and $FEF_{75\%}$ (representative of flow measures) (Table 17). Variation of the I/O exposure ratio from 0.2 to 0.5 had little effect on the regression coefficients obtained from the main model for hours above 60 ppb for both function measures. When the data from test session 2 were used instead of those from test session 1, the estimates of ozone effect were virtually identical.

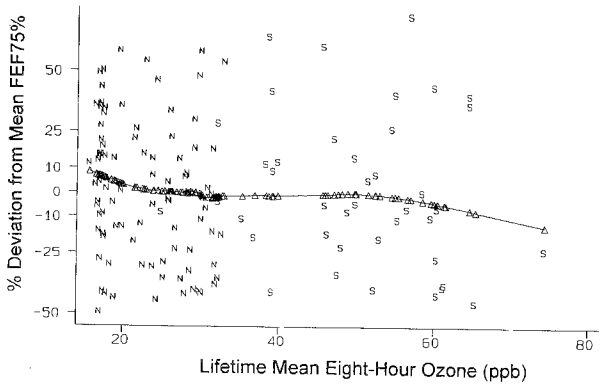


Figure 15. Residuals of $FEF_{75\%}$ derived from a regression of $FEF_{75\%}$ on age, height, sex, and region plotted against the effective lifetime ppb-hours. N = SFBA, S = LAB, Δ = smoothed data from LOESS smooth curve with 80% of data used to estimate each smoothed point.

Regardless of which covariates were included in the model, the coefficients for hours of ozone above 60 ppb were always negative for $FEF_{75\%}$. Once region and height were entered into the model, the other covariates had little effect. Region clearly had the largest effect, as the covariate combinations that included region resulted in the largest negative coefficients. For FEV_1, the model with no covariates reflects the larger volumes for students from LAB that are seen in Table 4. Addition of sex and height did not change the sign, but the addition of sex and ethnicity did result in a negative coefficient. This reflects the tendency toward smaller volumes in students of Asian descent (see Part I), who were overrepresented in the SFBA sample. In contrast to $FEF_{75\%}$, the effect of region was much less dramatic on the ozone coefficient for FEV_1.

Estimates of lifetime exposure to PM_{10} and NO_2 were derived with the ecologic approach that was used for ozone. Addition of lifetime estimates for exposure to PM_{10} resulted in a small decrease in the ozone effect estimates (based on I/O = 0.2) for both measures of function (11% for FEV_1 and 6% for $FEF_{75\%}$), but the effect estimate for $FEF_{75\%}$ remained statistically significant (Table 17). The addition of lifetime exposure to NO_2 to the model had virtually no impact on the ozone effect estimate. Combined addition of PM_{10}, NO_2, average temperature, and relative humidity did not change the ozone effect coefficient for FEV_1 but had a large effect on the ozone effect coefficient for $FEF_{75\%}$ (Table 17).

DISCUSSION

RELIABILITY OF QUESTIONNAIRE-BASED ESTIMATES OF LIFETIME EXPOSURE TO OZONE

The present investigation indicates that reproducible (reliable) estimates of lifetime exposure to ozone that are

Table 17. Tests of Sensitivity of Regression Coefficient for Effective Hours of Ozone Above 60 ppb on FEV_1 and $FEF_{75\%}$[a]

	FEV_1 (L)			$FEF_{75\%}$ (L/sec)		
Element Whose Sensitivity Is Tested	Regression Coefficient[b]	SE	r^2 from Regression	Regression Coefficient[b]	SE	r^2 from Regression
I/O ratio						
0.2	−.092	.085	.61	−.252[c]	.117	.18
0.5	−.118	.092	.61	−.271[c]	.127	.16
Test session 2 data						
I/O ratio = 0.2	−.144	.090	.63	−.324[c]	.126	.23
Model covariates[d]						
No covariates (crude)	+.022	.067	.001	−.064	.064	.01
Region, height	−.001	.096	.46	−.212[e]	.114	.16
Sex, region	−.072	.096	.45	−.246[c]	.116	.12
Sex, region, ethnicity	−.147	.091	.54	−.289[c]	.117	.15
Sex, height	+ .010	.044	.57	−.075	.060	.15
Sex, region, height	−.033	.086	.57	−.221[e]	.114	.17
Sex, ethnicity	−.036	.046	.60	−.101	.063	.16
Other pollutants[b]						
Main model + PM_{10}	−.083	.085	.61	−.237[c]	.117	.20
Main model + NO_2	−.096	.086	.61	−.257[c]	.118	.18
Main model + PM_{10} + NO_2 + temp. + humidity	−.100	.090	.62	−.173	.124	.22

[a] Test session 1 data were used for main model only for the same regressions shown in Table 15.

[b] Regression coefficient is for the effect of distribution of the standardized ozone effect on measure of lung function.

[c] $p \leq 0.05$.

[d] I/O ratio = 0.2 used for all models.

[e] $p \leq 0.1$.

based on questionnaire data in conjunction with an appropriate database of ambient ozone data can be obtained for adolescents and young adults.

Given that the fundamental step in the method used to assign an exposure value was based on interpolation of fixed-site ozone monitoring data to a residence, the quality of the residential history became the critical determinant of reproducibility of the lifetime exposure estimates. Although residential histories tended to become less reproducible as the number of residences increased, the effect of this lack of reproducibility on lifetime exposure estimates for ozone was relatively small when exposure assignments were determined without considering activity patterns (Figure 4; Table 14, ecologic model). This result is due largely to the fact that most of the unreliability could be attributed to residences of short duration, which received relatively low weights in the overall estimate (Equation 4). Obviously, this problem could be minimized by restricting samples to subjects who lived at the same residence for all of their lives. However, such an approach would be inefficient for the population studied, as only 29% of the sample had lived at a single residence (Table 5). Restricting the sample to those with up to two residences still would have reduced by 36% the number of available subjects. The interpolation method used to assign ambient concentrations to the residence requires only the accurate and reproducible specification of zip code. If simple efforts had been applied to resolve unreliable street names, another 8% of residences would have been classified as having reliable locations. As virtually all subjects could reliably report the years over which they lived at a residence, the reproducibility of location became the limiting factor in the overall reliability of residential history for the purposes of exposure assignment.

The questionnaire instrument addressed a number of other factors that relate to appropriateness of using home residence as the basic reference for exposure assignment. Approximately two-thirds of all of the schools that the subjects reported attending were within three miles of their residences. For approximately 60% of the residences where students reported being engaged in moderate or heavy activities, these activities were carried out within three miles of the residence. Finally, for approximately 80% of residences, subjects reported that they had not lived away from the residence (e.g., during vacation) for longer than two months during the months of May through October (months of highest ambient ozone concentrations). Thus, for this particular sample of adolescents, residence appeared to be a reasonable reference point for the most typical ambient ozone concentration to which individuals were exposed.

The effort to partition subjects' time into typical time spent indoors versus outdoors made use of a combination of two approaches. A baseline partition utilized data from a detailed study of the 24-hour activity patterns of a clustered, random-digit-dialing sample of all households in California, with the state divided into three strata: Los Angeles and the South Coast, the San Francisco Bay Area, and the rest of the state (Wiley et al. 1991b). The question structure of the questionnaire developed for the present investigation elicited responses that were intended to capture the median and upper and lower quartiles of the distribution of time spent indoors or outdoors (Appendix A, Main Questionnaire, question OD-1). Assignments based on these data represent a useful modification of typical ecologic assignments. The questions that were necessary for the ecologic assignments could be answered with a high degree of reproducibility, except that, for the age range less than 5 years, the number of "Don't remember" answers was large (data not shown).

The above ecologic assignment was supplemented with questions that were designed to permit estimates of the typical time that individuals spent engaged in outdoor activities of varying intensity. For both moderate and heavy activity categories, the reliability analysis indicated that more than 90% of subjects of the type used in this study would be expected to provide useful information on their activity patterns (Table 12). The reliability of the test-retest answers tended to decrease as the amount of activity reported increased (Figures 5 and 6). Neither the number of lifetime residences nor the length of the recall period affected the overall reliability (Table 13). An analysis that evaluated reliability of activity reporting for residences that were occupied at 12 years of age or younger showed similar reliability to reporting for residences in which the subject was older than 12 (data not shown). These data are consistent with a 10-year prospective study of the activity recall of 451 adults by Blair and coworkers (1991), who observed that activity recall did not decline over a 10-year interval. In the Blair study, correlations for activity recall for 60 leisure-time activities ranged from 0.35 to 0.64 for activities that would be classified as heavy in the present investigation. In another study, 873 adult males who were reexamined after 10 years and asked to recall their activity 10 years previously (Lee et al. 1992), the Spearman correlation coefficient for derived energy expenditure (kcal/day) was 0.38, with 45% of the variance being attributed to recall error. As in the present investigation, the Lee study recorded greater unreliability with increasing levels of activity.

Comparison of the reliability of the reporting of physical activity in the present investigation with the results of other

studies is limited due to differences in the methods of data collection, the test-retest protocols, and the relative lack of data of the type presented in Table 13 and in Figure 6. Thus, the comparisons that follow are based on reported correlation coefficients, which can provide misleading estimates of the level of agreement in within-individual comparison studies (Bland and Altman 1995). Most studies of the reproducibility of reports of physical activity focus on the correlations either for short intervals of activity assessed after relatively short time lags (e.g., recall of a single week's activity as assessed several days or weeks after the week under study) or, less frequently, for activity assessed after long periods of time as in the studies cited above (Blair et al. 1991; Lee et al. 1992). In contrast, the concern of the present study was the short-term reliability of recall of typical activity patterns over the lifetimes of the subjects. Nonetheless, qualitative comparisons between the findings of the present study and those of other published studies are useful.

Jacobs and coworkers (1993) evaluated the reliability of 10 commonly used physical activity questionnaires. A test-retest correlation of 0.60 was observed for total activity as assessed by a four-week activity history over a test-retest interval of one month. An assessment of the Minnesota Leisure Time Questionnaire over a one-year recall period gave test-retest correlations of 0.32 and 0.71 for moderate and heavy activities, respectively (Jacobs et al. 1993). Although the data for the present study showed differences in the same direction, the differences between the two classes of activity were much smaller (Tables 12 and 13). Part of the discrepancy between the studies may be related to the fact that the present study did not assess the repeatability of the reporting of specific activities, as did Jacobs and coworkers, but rather focused on classes of activities. As demonstrated in a published compendium of energy expenditure for physical activities (Ainsworth et al. 1993a), a specific activity may fall into different energy expenditure categories that depend on the intensity with which the activity is performed. This variability in the classification of activity based on energy expenditure will lead to less reliability in studies that assess specific activities. The present study reduced this source of unreliability through the use of somewhat broad classifications that combined elements of specific activities with their energy expenditures.

Blair and coworkers (1991) took another approach to assessing the reliability of activity reporting. They classified total leisure time energy expenditure in kilocalories into quintiles, and "agreement" was defined as classification within the same or an adjacent quintile. For 10-year recall, agreement ranged from 59% to 72% across all activity levels. In the present study, creation of quintiles for time (hours/month) engaged in activity resulted in agreement in 83% and 85% of records for moderate and heavy activity, respectively (data not shown). Similar approaches have been taken for the assessment of the reliability of dietary recall (Willett et al. 1985). In the case of serum cholesterol values, 75% of subjects demonstrated agreement, but only 38% of results matched exactly on quintile. In the present study, 50% of records were in the same quintile for time (hours/month). Block and coworkers (1990) have provided a summary of test-retest correlations for a variety of measurements: 0.6 to 0.8 for reported nutrient intake from dietary records, 0.59 for serum cholesterol values, 0.67 to 0.70 for blood pressure in adults, and 0.49 to 0.65 for body mass index (weight/height^2). Correlations of reported body weight over a 10-year period have been estimated as 0.73 and 0.74 for males and females, respectively (Perry et al. 1995). Thus, the correlation estimates for repeatability of the reporting of typical lifetime activity in the present investigation (Table 13, $Mean_{diff}$) compare favorably with those observed in other settings for a variety of questionnaire-derived and directly measured characteristics.

Although reliability is a prerequisite for any measurement tool, estimates of reliability provide only estimates of the correlation of an observed measure with the true value (Armstrong et al. 1994) under a classic error model (Thomas et al. 1993); that is, reliability does not provide a direct estimate of validity. Obviously, the validity of the estimates of the time spent outdoors and the types of activity bears heavily on the validity of the estimates of effective lifetime exposure to ozone. There is no way to validate directly the estimates that have been provided. Even studies that use personal ozone monitors to assess short-term exposure are dependent on questionnaires (usually daily diaries) for the location of the subjects over various time periods (Liu et al. 1993) and would be dependent on questionnaire data on activities if the intent were to infer dose to the lung. An indirect approach to assessing the validity of the estimates presented is to compare them with published estimates of time spent in leisure activities as determined in short-term, diary-based studies, which, short of direct observation (which is not feasible), provide the most accurate questionnaire-based assessment that is feasible. Spier and coworkers (1992) collected daily diary data from elementary and high school students in Southern California. Ventilation rates were used to classify activity levels; their "medium" and "fast" categories most closely approximated the moderate and heavy categories in the present study (the "medium" category in the Spier study) probably included some lower-intensity activities than the moderate category in this study). High school students reported 45.4 hours/month of activity on "warm" and "fair" days in September and October. When analyses in the present study were restricted to

residences occupied at age 12 years or older, an arithmetic mean of 46.6 hours/month (geometric mean 33.5 hours/month, as distribution was skewed to the left—data not shown) was observed for the sum of the two activity classes. A similar daily diary study by Schwab and coworkers (1991) reported 51 hours/month of "medium" or "active" activity for high school students. This latter study also was likely to have included lower levels of activity than were sought in the present study. On the basis of these data, it appears that this study has provided unbiased estimates of the typical time, over a lifetime, that the subjects spent outdoors in activities of varying intensity.

One limitation of the method that was used relates to the fact that various periods of life were all referenced to specific residences. Therefore, the effect of age on the reliability of the activity reporting could not be assessed directly. When the data were stratified by mean age at a residence, there was a low prevalence of doers and a high prevalence of "Don't remember how much" for those residences that were no longer occupied by age 6 (Table 10). The degree to which the between-residence variance component for hours/month of activity (Table 13) is confounded by age effects cannot be determined with certainty. Other data (Jenkins et al. 1992) support the conclusion that a substantial amount of the between-residence variance results from the confounding effect of age on time outdoors and activity patterns. Given the importance of age as a determinant of activity patterns and time spent outdoors (Wiley et al. 1991b), it may have been desirable to include an activity assessment that was specifically referenced to given age periods of life and to link this with the residential histories. However, such an approach would have created its own difficulties with regard to the precise relation between age intervals and residences. Given the importance of residence as a reference for the use of the ambient monitoring data, the approach taken seems to be the most appropriate one. A useful supplement to the questions that actually were used would have been to ask the subjects how old they were at the time they lived at the residence as a memory aid for the questions about activity patterns. That the question structure actually used created difficulties for subjects is indicated by the fact that 20% of residence-specific questionnaires reported years of activity that exceeded the duration over which the student lived at the residence.

The data in Figures 5 and 6 indicate that the errors of the estimates of time spent in activity are correlated with the levels of the estimates. As such, the correlation coefficients in Table 13 provide estimates of the upper bound (lower bound unspecified) of the square of the correlation (validity coefficient) between the true activity levels of the subjects and those estimated by the questionnaires (Armstrong et al. 1994). As derived from the values in column r_p of Table 13, the upper-bound estimates for the validity coefficients are 0.85 and 0.80 for moderate and heavy activity, respectively.

Given that the estimates of ELT exposures for ozone (Table 14) are heavily influenced by the zip code–specific estimates of the ambient ozone, which, in turn, have been treated as if they are measured without error, the most realistic assessment of the effects of the measurement error of these estimates can be provided by treating the activity data as the effective exposure variable. To account for the correlation between the error and the level of activity, the formulation presented by Wacholder (1995) is followed. As summarized by Wacholder, the bias factor associated with an imperfectly measured variable is a function of (1) the correlation, ρ, of the level of the true value of the variable, X (outdoor exposure to ambient ozone; here measured as hours/month spent in activity as a surrogate, Z), and the error, E, in the measurement of X; (2) the ratio of the error variance, Var(E), to the variance of X, Var(X). As a consequence of these two factors and the error model that is considered, the regression coefficients for the effect of X on an outcome (e.g, in this study, various measures of lung function) can be biased in either direction or not biased at all. Under a Berkson error model (Thomas et al. 1993) (which could be considered as plausible for the time outdoors models, which used the CARB-derived population-based median and quartile values), there would be no bias in the regression coefficient. However, the entire approach taken in the formulation of the ELT exposure and the preliminary evaluation of the relation between ELT exposure and pulmonary function is more in keeping with a classic error model (Thomas et al. 1993). The usual expectation of bias toward the null under the classic error model holds only when $\rho = 0$, which is not the case for these data. If it is assumed that the variance estimates for time spent in activities, Var(Z), estimates Var(X), then Var(E) (Table 13, last column) is smaller than Var(Z) (Table 13, sum of between-subject and between-residence variance), with all but one value of the ratio Var(E)/Var(X) being less than 0.6. Thus, based on a ratio of less than 0.6 and ρ greater than 0, regression coefficients for ELT exposure would be biased toward the null, with estimated attenuation for these data in the range of 0.5 to 0.6 (Wacholder 1995). If, on the other hand, time spent in activities had been treated as a potential confounder and had not been incorporated in the estimate for ELT exposure to ozone, then its effect on outcomes such as lung function would have been less predictable (Wacholder 1995), given observed correlation between the

error and the level of activity. Thus, it would appear to be preferable for epidemiologic studies of the long-term health effects of exposure to ambient ozone to derive composite exposure measures as was done in this study.

All of the approaches used provided highly reproducible estimates of lifetime exposure to ozone (intraclass correlations all greater than 0.9, Table 14). Not surprisingly, the approach that used all of the activity history had the lowest reliability, especially when the 10 am to 6 pm average was used as the metric. As noted previously, this high overall level of reliability is driven largely by the residence-based method that was chosen. Thus, the greatest difference in the methods relates to the magnitude of the estimates of "typical" exposure over a lifetime for each metric, which is a function of the procedure used to estimate time spent outdoors. Although the issue of magnitude is clearly important for setting environmental standards, absolute magnitude may not be as important as relative magnitude in the application of the estimates of each approach to etiologic inference—that is, each of these approaches would be expected to yield similar effect relations (adjusted for scale) with the lung function outcomes that were the consequence of long-term exposure.

Another potential limitation of the approach taken relates to the interval of five to seven days between the test and retest. The choice of interval was motivated largely by the need for a relatively short time between pulmonary function tests. The relative shortness of the interval does raise the question of whether the estimates of reliability have been biased upward as a result of students "remembering" their answers from the first test. Although this possibility cannot be fully excluded, several observations suggest that any such effect was small: 20% to 30% of subjects with three or more residences could not reliably report the month and year of all of their residences (Table 6); approximately 20% of subjects could not provide reliable data on the number of times and sessions per time that they performed moderately intense physical activity (Table 9); and the between-test variance accounted for 35% of the total variance for heavy activities (Table 13).

PRELIMINARY ANALYSIS OF THE RELATION BETWEEN ESTIMATED LIFETIME EXPOSURE TO AMBIENT OZONE AND MEASURES OF PULMONARY FUNCTION

This is the first study to attempt to relate a direct estimate of cumulative lifetime exposure to ozone to measures of pulmonary function. Despite the small sample size of this feasibility study, consistently negative point estimates for the effect of ELT exposure to ozone were observed for $FEF_{25\%-75\%}$ and $FEF_{75\%}$, with all of the effect estimates for hours above 60 ppb being statistically significant for $FEF_{75\%}$. That each of the approaches gave a consistent "ranking" of small airway function in relation to exposure is indicated by the consistency of the point estimates of the regression coefficients for the standardized estimates of ELT exposure. In contrast to the findings for the flow measures, the relation between ELT exposures and FVC were inconsistent and never statistically significant. The results for FEV_1 were somewhat more consistent than those for FVC but considerably less so than for the flow measures. This is not surprising, given that, in these healthy adolescents, FEV_1 can be expected to encroach well into the effort-independent portion of MEFV curves (Bates 1989) and to include the entire portion of the curve that defines $FEV_{25\%-75\%}$ and, for most subjects, the part of the curve that defines $FEF_{75\%}$: mean (± SD) FEV_1/FVC ratio = 87% (± 6%). The slope of phase III from the SBNW curve was unrelated to ELT exposure to ozone, and many of the regression coefficients had negative signs (decreased slope with increased exposure) instead of the expected positive signs (increased slope with increased exposure). Slope of phase III has been shown to have a within-subject variance that is approximately 24% of total variance compared with 5% and 9% for $FEF_{25\%-75\%}$ and $FEF_{75\%}$, respectively (see Part I of this Research Report). This increased variance makes ΔN_2 a much less efficient measure for epidemiologic studies and, to some extent, accounts for the lack of statistically significant effects of ozone exposure and the marked instability of the exposure estimates for this measure.

The overall results presented above are completely consistent with the functional consequences that would be predicted for associations between long-term exposure and lung function response based on the presumed dosimetry of ozone in the human lung (U.S. Environmental Protection Agency 1986, 1995). Studies in animals experimentally exposed to ozone at various concentrations and for varying periods of time suggest that the principal site of morphologic damage is in the centriacinar region of the lung (junction of the conducting airways with the gas exchange regions) (U.S. Environmental Protection Agency 1986, 1992b; Collaborative Ozone Project Group 1995). Acute and chronic inflammation as well as remodeling have been observed in the centriacinar regions (U.S. Environmental Protection Agency 1992b, 1995).

Of particular interest in terms of possible chronic effects of exposure is the concomitant occurrence of inflammation (respiratory bronchiolitis) and remodeling in the centriacinar region (changes in cell populations and interstitial collagen) (U.S. Environmental Protection Agency 1995). Recent theoretical models of ozone dosimetry in humans suggest that maximum doses to the lung of inhaled ozone

occur at the level of the terminal bronchioles (U.S. Environmental Protection Agency 1995). A considerable body of physiologic data has established that flow rates measured during the terminal portion of a maximum forced expiratory maneuver ($FEF_{75\%}$ and to a substantial degree $FEF_{25\%-75\%}$) are largely governed by the properties (geometry, compliance, and tethering effect of surrounding lung parenchyma) of airways smaller than 2 mm in diameter (Hyatt 1983), which approximate the centriacinar region of the lung. A similar interpretation is given to ΔN_2 (Bates 1992), but some controversy remains as to the physiologic interpretation of this test (Paiva and Engel 1987). The relevance of flows at low lung volumes as appropriate measures of ozone effect is further strengthened by the exposure chamber studies of Weinmann and coworkers (1995a,b). These investigators demonstrated ozone-induced reductions in volume-corrected $FEF_{25\%-75\%}$ that were of greater magnitude and persistence than those observed for FVC and FEV_1. Moreover, these investigators observed that the slope of the MBNW test was too variable to provide the same consistency of effects as did $FEF_{25\%-75\%}$ (Weinmann et al. 1995b). This is in keeping with the substantially greater variability (relative to flows from the MEFV curve) observed for ΔN_2 as part of this study (see Part I). The data that suggest that FVC responses observed in chamber exposure studies are the result of neurally mediated reductions in vital capacity (Hazucha and Bates 1989) would suggest that this measure of lung function should not be related to long-term exposure to ambient concentrations of ozone.

The data presented indicate two features of the ELT exposure–lung function association of potential importance. First, the estimated magnitude of effect of a difference of 1 SD in ELT exposure is above that estimated for the effects of exposure to environmental tobacco smoke (U.S. Environmental Protection Agency 1992a). Second, estimated exposures over the early years of life (Table 16) appear to lead to reductions in flows that may be greater than exposures cumulated over later years. This latter observation would suggest that underlying response function is not truly linear and that younger individuals may be more susceptible to exposures to increasing levels of ambient ozone. The preliminary nature of the present investigation and the wide confidence intervals around the point estimates make these inferences highly tentative but clearly suggest the need for further study.

Several issues are relevant to the interpretation of the pulmonary function results. The univariate analyses did not show any relation between flow measures and exposure (Table 17, No covariates). This resulted from the strong confounding effect of area of residence, sex, and ethnicity. Although LAB and SFBA did not differ significantly in the percentage of females in their respective samples (Table 4), 66% of all females (39/53) were from SFBA with its markedly lower ambient ozone concentrations (Figure 1). Similarly, students of Asian ethnicity (with generally lower levels of lung function) also were numerically overrepresented in the SFBA sample (Table 4). The fact that region had a strong effect on the regression coefficient for ozone effect (Table 17) suggests that residual confounding related to sex, ethnicity and other unmeasured covariates (e.g., differences in past exposure to environmental, especially maternal, tobacco smoke) is being captured by this variable. Differences in ELT exposure to PM_{10} and NO_2, when considered singly, did not appear to be responsible for the effects observed, although the random error in these exposure estimates may have been greater than for ozone due to a less-dense monitoring network, especially for PM_{10}. A model that contained PM_{10}, NO_2, temperature, and humidity did show a reduction in the regression coefficient. The extent to which the change in the ozone effect coefficient was related to the doubling of the number of parameters in the model or to some meaningful effect of temperature and humidity cannot be determined with any certainty. More than likely the considerable colinearity of temperature with ozone accounts for some of this reduction.

Despite the nearly nonoverlapping distributions of ozone exposure metrics and their lifetime estimates between LAB and SFBA (Figures 1 and 9 through 12), the response function appeared to be reasonably linear. Simple regression diagnostics (Appendix D) suggested that a linear model provided a reasonable summary of the relation. Similarly, a plot of $FEF_{75\%}$ residuals from a regression of $FEF_{75\%}$ on age, height, sex and region (exposure metric omitted) versus the effective lifetime ppb-hours based on the main model (Figure 15) suggested that a linear summary was appropriate across the entire range of exposure. Given the limited sample size and the preliminary nature of these findings, it would not be appropriate to make strong inference on the shape of any effective exposure–response association, a point alluded to previously in relation to differences in point estimates over different epochs of life (Table 16). It does appear appropriate to conclude that the relations observed in these data are not the result of the choice of the regression model, which leaves open the question about the overall approach that was used to assign the lifetime exposures. However, the method used follows the basic principles of microenvironment-based exposure assignment, which is in keeping with contemporary concepts of exposure modeling (Lurmann et al. 1989).

The failure to find any relation between the various ELT exposure metrics for ozone and ΔN_2 is contrary to expectations from the reported findings for the studies of Detels and

coworkers (1987). The small sample size of the present study and the much greater within-subject variability of this test relative to that for the flow measures (see Part I) could explain the failure to observe any effect. However, given the greater time and cost of equipment required to obtain measures of ΔN_2, the substantial variability of the test, and the remaining uncertainty about the physiologic interpretation, there seems little reason or need to consider this measure for use in epidemiologic studies of effects of long-term exposure to ambient ozone (and other pollutants).

CONCLUSIONS

The results of this study clearly indicate that epidemiologic studies of the health effects of long-term exposure to increased ambient levels of ozone are feasible in populations of adolescents and young adults. The analyses indicate that such studies can be conducted in locations where relatively dense monitoring networks for ozone exist and for which there is a reasonable historical record of ambient data for ozone and other pollutants whose effects could confound any observed relations. For the purposes of etiologic inference, it appears that the minimum epidemiologic data needed are accurate lifetime residential histories. For purposes more closely related to the public health issues of setting standards for air quality, data on typical outdoor activity patterns may be useful. The latter type of data can be obtained with a level of reliability that is comparable to many exposure measures that are in use in epidemiologic studies of a wide variety of health outcomes for which public health recommendations on exposure (e.g., diet, physical exercise) have been developed. Moreover, the data presented indicate that the estimates of typical activity patterns over the lifetime of adolescents are reasonably accurate and may be used to provide valid quantitative estimates of long-term exposure.

ACKNOWLEDGMENTS

The authors acknowledge the superb technical assistance of Liz Cragen, who carried out all of the recruitment and testing of the subjects, and the assistance of Greg Thompson, Director, Office of Student Research, University of California, Berkeley, who provided student-related address data.

The authors especially acknowledge David Bates for his thoughtful comments and critique during all phases of this work.

REFERENCES

Abbey D, Mills P, Petersen F, Beeson W. 1991a. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ Health Perspect 94:43–50.

Abbey D, Moore J, Petersen F, Beeson L. 1991b. Estimating cumulative ambient concentrations of air pollutants: Description and precision of methods used for an epidemiologic study. Arch Environ Health 46:281–287.

Abbey D, Petersen F, Mills P, Beeson W. 1993. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. Arch Environ Health 48:33–46.

Agresti A. 1990. Categorical Data Analysis. John Wiley & Sons, New York, NY.

Ainsworth B, Haskell W, Leon A, Jacobs D, Montoye H, Sallis J, Paffenbarger R Jr. 1993a. Compendium of physical activities: Classification of energy costs of human physical activities. Med Sci Sports Exercise 25:71–80.

Ainsworth B, Jacobs D, Leon A. 1993b. Validity and reliability of self-reported physical activity status: The Lipid Research Clinics questionnaire. Med Sci Sports Exercise 25:92–98.

Altman D, Bland J. 1983. Measurement error in medicine: The analysis of method comparison studies. Statistician 32:307–317.

Armstrong B, White E, Saracci R. 1994. Principles of Exposure Measurement in Epidemiology. Oxford University Press, New York, NY.

Avol E, Estes M, Navidi W, Colome S, Lurmann F, et al. 1995. Residential Microenvironmental and Personal Sampling Project for Exposure Classification. University of Southern California, School of Medicine, Pasadena, CA.

Bates D. 1989. Respiratory Function in Disease, 3rd ed. WB Saunders Co., Philadelphia, PA.

Bates D. 1992. Historical introduction: The evolution of understanding of the small airways. Semin Respir Med 13:63–71.

Becker M, Agresti A. 1992. Log-linear modeling of pairwise interobserver agreement on a categorical scale. Stat Med 11:101–114.

Blair S. 1984. How to Assess Exercise Habits and Physical Fitness. John Wiley & Sons, New York, NY.

Blair S, Dowda M, Pate R, Kronenfeld J, Howe H, Parker G, Blair A, Fridinger F. 1991. Reliability of long-term recall of participation in physical activity by middle-aged men and women. Am J Epidemiol 133:266–275.

Bland J, Altman D. 1995. Comparing two methods of clinical measurement: A personal history. Int J Epidemiol 24(3):S7–S14.

Block G, Woods M, Potosky A, Clifford C. 1990. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 43:1327–1335.

Calderon-Garciduenas L, Osorno-Valezquez A, Bravo-Alvarez H, Delgado-Chavez R, Barrios-Barquez R. 1992. Histopathologic changes of the nasal mucosa in southwest metropolitan Mexico City inhabitants. Am J Pathol 140:225–232.

Calderon-Garciduenas L, Roy-Ocotla G. 1993. Nasal cytology in southwest metropolitan Mexico City inhabitants: A pilot intervention study. Environ Health Perspect 101:138–144.

California Air Resources Board Technical Support Division. 1990. California Air Quality Data Summary of 1990 Air Quality Data: Gaseous and Particulate Pollutants. California Air Resources Board, Sacramento, CA88.

Chinn S, Burney P. 1987. On measuring repeatability of data from self-administered questionnaires. Int J Epidemiol 16:121–127.

Cicchetti D, Feinstein A. 1990. High agreement but low kappa: Part II. Resolving the paradoxes. J Clin Epidemiol 43:551–558.

Collaborative Ozone Project Group. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies, Part XI, Integrative Summary. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Delcourt C, Cubeau J, Balkau J, Papoz L, CODIAB-INSERM-ZENCA Pharma Study Group. 1994. Limitations of the correlation coefficient in the validation of diet assessment methods. Epidemiology 5:518–524.

Detels R, Rokaw S, Coulson A, Tashkin D, Sayre J, Massey F Jr. 1979. The UCLA population studies of chronic obstructive respiratory disease: I. Methodology and comparison of lung function in areas of high and low pollution. Am J Epidemiol 109:33–58.

Detels R, Tashkin D, Sayre J, Rokaw S, Coulson A, Massey F Jr, Wegman D. 1987. The UCLA population studies of chronic obstructive respiratory disease: Part 9. Lung function changes associated with chronic exposure to photochemical oxidants; a cohort study among never smokers. Chest 92:594.

Division of Lung Diseases, National Heart, Lung and Blood Institute. 1973. Suggested standardized procedures for closing volume. National Heart, Lung and Blood Institute, Bethesda, MD.

Duan N. 1982. Models for human exposure to air pollution. Environ Int 8:305–309.

Feinstein A, Cicchetti D. 1990. High agreement but low kappa: I. The problems of two paradoxes. J Clin Epidemiol 43:543–549.

Fleiss J. 1981. Statistical Methods for Rates and Proportions. John Wiley & Sons, New York, NY.

Graham P, Jackson R. 1993. Primary versus proxy respondents: Comparability of questionnaire data on alcohol consumption. Am J Epidemiol 138:443–452.

Hazucha M, Bates D. 1989. Mechanism of action of ozone on the human lung. J Appl Physiol 67:1535–1541.

Health Effects Institute. 1994. Environmental Epidemiology Planning Project. HEI Communication Number 3. Health Effects Institute, Cambridge, MA.

Hodgkin J, Abbey D, Euler G, Magie A. 1984. COPD prevalence in nonsmokers in high and low photochemical air pollution areas. Chest 86:830–838.

Hyatt R. 1983. Expiratory flow limitation. J Appl Physiol 55:1–8.

Jacobs D, Ainsworth B, Hartman T, Leon A. 1993. A simultaneous evaluation of ten commonly used physical activity questionnaries. Med Sci Sports Exercise 25:81–91.

Jenkins P, Phillips T, Mulberg E, Hui S. 1992. Activity patterns of Californians: Use of and proximity to indoor pollutant sources. Atmos Environ 26:2141–2148.

Kinney P, Hayes C, Butler R, Lippmann M. 1992. Pulmonary function of military academy freshmen from areas of high and low ozone levels: Preliminary results. In: Trophospheric Ozone and the Environment: II. Effects of Modeling and Control, pp. 203–218. Air & Waste Management Association, Atlanta, GA.

Kleinman M. 1991. Effects of ozone on pulmonary function: The relationship of response to dose. J Expos Anal Environ Epidemiol 1:309–325.

Krowka M, Enright P, Rodarte J, Hyatt R. 1987. Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis 136:829–833.

Landis J, Kock G. 1977. The measurement of observer agreement for categorical data. Biometrics 33:159–174.

Laporte R, Montoye H, Caspersen C. 1985. Assessment of physical activity in epidemiologic research: Problems and prospects. Public Health Rep 100:131–146.

Lee M, Whittemore A, Jung D. 1992. Reliability of recalled physical activity, cigarette smoking and alcohol consumption. Ann Epidemiol 2:705–714.

Liu L-JS, Koutrakis P, Suh H, Mulik J, Burton R. 1993. Use of personal measurements for ozone exposure assessment: A pilot study. Environ Health Perspect 101:318–324.

Lurmann F, Winer A, Colume S. 1989. Development and application of a new regional human exposure (REHEX) model. EPA/A&WMA Specialty Conference—Total Exposure Assessment Methodology, November 4–7, 1989, Las Vegas, NV.

Ostro B, Lipsett M, Mann J, Krupnick A, Harrington W. 1994. Air pollution and respiratory morbidity among adults in southern California. Am J Epidemiol 137:691–700.

Ostro B, Lipsett M, Wiener M, Selner J. 1991. Asthmatic responses to airborne aerosols. Am J Public Health 81:694–702.

Ott W. 1982. Concepts of human exposure to air pollution. Environ Int 7:179–196.

Paiva M, Engel L. 1987. Theoretical studies of gas mixing and ventilation distribution in the lung. Physiol Rev 67:750–796.

Perry G, Byers T, Mokdad A, Serdula M, Williamson D. 1995. Validity of self-reports of past body weights by U.S. adults. Epidemiology 6:61–66.

SAS Institute Inc. 1989a. SAS/FSP Software: Usage and Reference Version 6, 1st ed. SAS Institute Inc., Cary, NC.

SAS Institute Inc. 1989b. SAS/STAT User's Guide, Version 6, 4th ed. SAS Institute Inc., Cary, NC.

Schwab M, Terblanche A, Spengler J. 1991. Self-reported exertion levels on time/activity diaries: Application to exposure assessment. J Expos Anal Environ Epidemiol 1:339–356.

Schwartz J. 1989. Lung function and chronic exposure to air pollution: A cross-sectional analysis of NHANES II. Environ Res 50:309–321.

Spier C, Little D, Trim S, Linn W, Hackney J. 1992. Activity patterns in elementary and high school students exposed to oxidant pollution. J Expos Anal Environ Epidemiol 2:277–293.

Stata Corp. 1993. STATA Release 3.1 Reference Manual. Stata Corp., College Station, TX.

Stern B, Jones L, Raizenne M, Burnett R, Meranger J, Franklin C. 1989. Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. Environ Res 49:20–39.

Stern B, Raizenne M, Burnett R, Jones L, Kearney J, Franklin C. 1994. Air pollution and childhood respiratory health: Exposure to sulphate and ozone in ten Canadian rural communities. Environ Res 66:125–142.

Tager IB. 1993. Summary of papers and research recommendations of Working Group on Tropospheric Ozone, Health Effects Institute Environmental Epidemiology Planning Project. Environ Health Perspect 101(Suppl 4):237–239.

Taylor H, Jacobs D, Schucker B, Knudsen J, Leon A, Debacker G. 1978. A questionnaire for the assessment of leisure time physical activities. J Chronic Dis 31:741–755.

Thomas D, Stram D, Dwyer J. 1993. Exposure measurement error: Influence on exposure-disease relationships and methods of correction. Annu Rev Public Health 14:69–93.

U.S. Environmental Protection Agency. 1986. Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vol. 4. Environmental Criteria and Assessment Office, Washington, DC.

U.S. Environmental Protection Agency. 1992a. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. EPA-600/6-90/006F. Office of Research and Development, Washington, DC.

U.S. Environmental Protection Agency. 1992b. Summary of Selected New Information on Effects of Ozone on Health and Vegetation: Supplement to 1986 Air Quality Criteria for Ozone and Other Photochemical Oxidants. Environmental Criteria Assessment Office, Research Triangle Park, NC.

U.S Environmental Protection Agency. 1996. Air Quality Criteria for Ozone and Related Photochemical Oxidants, Vol. 3. Office of Research and Development, Washington, DC.

Wacholder S. 1995. When measurement errors correlate with truth: Surprising effects of non-differential misclassification. Epidemiology 6:157–161.

Weinmann G, Bowes S, Gerbse M, Kimball A, Frank R. 1995a. Response to acute ozone exposure in healthy men: Results of a screening procedure. Am J Respir Crit Care Med 151:33–40.

Weinmann G, Weidenbach-Gerbase M, Foster W, Zacur H, Frank R. 1995b. Evidence for ozone-induced small-airway dysfunction: Lack of menstrual-cycle and gender effects. Am J Respir Crit Care Med 152:988–996.

Wiley J, Robinson J, Cheng Y-T, Piazza T, Stork L, et al. 1991a. Study of Children's Activity Patterns. Research Division, California Air Resources Board, Sacramento, CA.

Wiley J, Robinson J, Piazza T, Garrett K, Cirksena K, et al. 1991b. Activity Patterns of California Residents. Research Division, California Air Resources Board, Sacramento, CA.

Willett W, Sampson L, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. 1985. Reproducibility and validity of a semiquantitative food frequency questionnare. Am J Epidemiol 122:51–65.

APPENDIX A. QUESTIONNAIRES

The Eligibility Questionnaire, Main Questionnaire, Detailed Activity List, and PFT Eligibility Form are included. A separate Main Questionnaire was completed for each residence. A PFT Eligibility Form was completed before each pulmonary function test session.

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES

ELIGIBILITY QUESTIONNAIRE

INSTRUCTIONS:
Please use a pencil to complete the questionnaire. Answer each question by either completely filling in the circle near your answer or writing in the information requested. If you make a mistake, erase as completely as you can. If you have any questions, please ask for clarification when the questionnaire is reviewed with you.

PERSONAL DATA
PLEASE PRINT CLEARLY

1. NAME: _____ (First M.I. Last)

LOCAL ADDRESS:

2a. ON CAMPUS: _____ (Mail Address)

or

2b. OFF CAMPUS: _____ (Street City Zip Code)

3. PHONE NUMBER: (____) _____ - _____

4. GENDER: ○ FEMALE ○ MALE

5. DATE OF BIRTH: _____ / ____ / 19____ (Month Day)

6. ETHNIC/RACIAL BACKGROUND:

○ CAUCASIAN
○ ASIAN or PACIFIC ISLANDER
○ HISPANIC
○ AFRICAN-AMERICAN
○ NATIVE AMERICAN
○ OTHER _____ (Specify)

OFFICE USE ONLY:

ID: _____ DATE: ____/____/____ (MM DD YR) TIME: ____:____ (24 HR.)

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
ELIGIBILITY QUESTIONNAIRE

BRIEF MEDICAL HISTORY

7. Has a doctor ever told you that you have or have had asthma?
○ No ○ Yes

8. In the past 12 months, have you had attacks of wheezing that made you feel short of breath?
○ No ○ Yes

9. Do you ever have episodes of wheezing at a time when you do not have a cold?
○ No ○ Yes

BRIEF SMOKING HISTORY

10. Have you ever smoked...
a. Cigarettes?
○ No ○ Yes, in past ○ Yes, currently
b. Marijuana?
○ No ○ Yes, in past ○ Yes, currently

IF "NO" TO BOTH, SKIP TO QUESTION 13

11. Have you ever smoked as much as 1 cigarette per day for a year or as many as 20 packs in your lifetime?
○ No ○ Yes

IF YOU ANSWERED "YES" YOU CAN STOP. THANK YOU FOR YOUR HELP.

12. Have you ever smoked as many as 3 joints per week for at least 6 months?
○ No ○ Yes

IF YOU ANSWERED "YES" YOU CAN STOP. THANK YOU FOR YOUR HELP.

DETAILED RESIDENTIAL HISTORY

13. Are you a lifelong resident of California? (i.e., never lived outside of California for more than 3 consecutive months).
○ No ○ Yes

IF YOU ANSWERED NO, YOU CAN STOP. THANK YOU FOR YOUR HELP.

14. Between the time that you graduated from high school and the time that you came to U.C. Berkeley, did you live away from home for more than 3 months?
○ Yes ○ No

! IF YES,
a. For how long did you live away?
____ ____ MONTHS
b. How many of these months were between May and October?
____ ____ NUMBER OF MONTHS
c. Where was this place?
_____ City/Town
_____ State (Country, if foreign)

15. Do you have a driver's license?
○ Yes ○ No

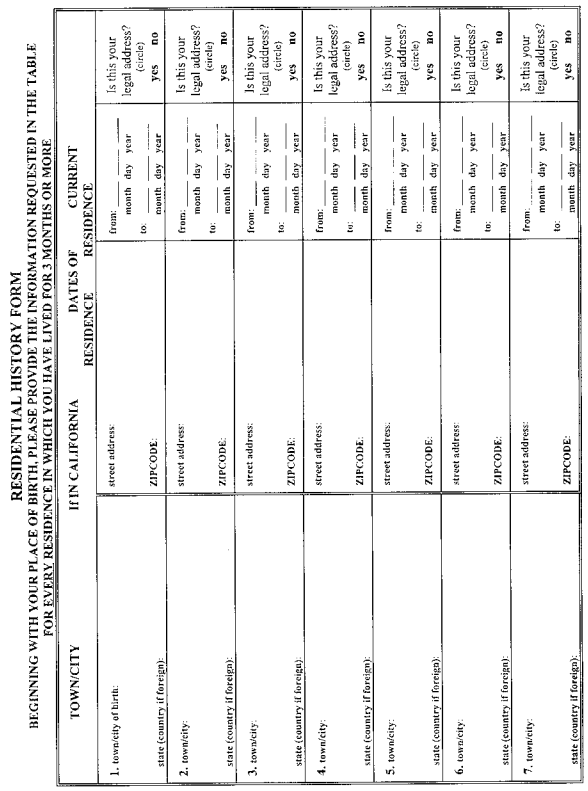
! IF YES,
a. In what year did you first get your driver's license?
19____

Please complete the "Residential History Form" on the next page. Begin with your place of birth. Please provide the information for every residence in which you have lived for at least 3 months.

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
ELIGIBILITY QUESTIONNAIRE

Office Use Only:

Eligibility ○ No ○ Yes ○ Yes, R
Informed consent signed ○ Y



RESIDENTIAL HISTORY FORM

BEGINNING WITH YOUR PLACE OF BIRTH, PLEASE PROVIDE THE INFORMATION REQUESTED IN THE TABLE FOR EVERY RESIDENCE IN WHICH YOU HAVE LIVED FOR 3 MONTHS OR MORE

	TOWN/CITY IF IN CALIFORNIA	DATES OF CURRENT RESIDENCE	Is this your legal address? (circle)
1.	town/city of birth:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
2.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
3.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
4.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
5.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
6.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		
7.	town/city:	from: month day year	yes no
	state (country if foreign)	to: month day year	
	street address:		
	ZIPCODE:		

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES

MAIN QUESTIONNAIRE (V2A)

This questionnaire is organized around the various residences that you identified on the "Eligibility Questionnaire" which you have already completed. Each residence that you have identified has been transcribed onto one of these forms. You should complete one form for each residence.

In your case, you need to complete _____ of these forms.

RECORD THE TIME THAT YOU START:_____ AND STOP:_____

I.D. _____

DATE ____/____/____
MM DD YR

RESIDENCE # ___ OF ___ RESIDENCES REPORTED

STREET ADDRESS:

_____

CITY/TOWN _____ ZIP CODE _____

DATES OF RESIDENCE:

From _____ To _____

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

NEIGHBORHOOD

R1-1. Which of the following best describes the type of structure in which you live (lived) at this residence?

- ○ Single family - unattached to another house
- ○ Single family - attached to another house
- ○ Building for 2-4 families
- ○ Building for 5-10 families
- ○ Building for more than 10 families
- ○ Mobile home or trailer
- ○ Boat, van, car
- ○ Other_____(Specify)
- ○ Don't remember

R1-2 Which of the following best characterizes the neighborhood in which this residence is (was) located?

- ○ Mostly single family homes widely spaced
- ○ Mostly single family homes close to each other
- ○ Mostly multiple family homes
- ○ A mixture of single and multiple family homes
- ○ Don't remember

R1-3 Which of the following best describes the neighborhood in which this residence is (was) located?

- ○ Rural or small town road/street used mainly by residents
- ○ Rural or small town road/street used mainly by through traffic
- ○ Suburban road/street used mainly by residents
- ○ Suburban road/street used by through traffic
- ○ City street used mainly by residents
- ○ City street used as a through street

R1-3a The traffic on this street is (was) best described as:

- ○ Heavy
- ○ Moderate
- ○ Light
- ○ Don't remember

R1-4 At the intersection closest to this residence is (was) there a...

- ○ Traffic light
- ○ Stop sign
- ○ Flashing traffic signal
- ○ "Yield" sign
- ○ None of the above
- ○ Don't remember

HOME CHARACTERISTICS

R1-5 Does (did) this home at this residence have air conditioning?

○ Yes ○ No ○ Don't remember

↓ IF YES:

a. What types of air conditioning does (did) it have? (MARK ALL THAT APPLY)

- ○ Central
- ○ Room
- ○ Swamp or evaporative cooler
- ○ Don't remember

b. During the months of May through October, how often is (was) the air conditioning on at least part of the day?

- ○ Never
- ○ Less than 14 days
- ○ 14-28 days
- ○ More than 28 days
- ○ Don't remember

R1-6 During the months of May through October, does (did) your family usually use a fan placed in a window or an attic fan to cool this home?

- ○ Yes
- ○ No
- ○ Don't remember

R1-7 When you lived in this home, are (were) the windows kept mostly shut during...

Jan-Feb	○ No	○ Yes	○ Don't Remember
Mar-Apr	○ No	○ Yes	○ Don't Remember
May-June	○ No	○ Yes	○ Don't Remember
July-Aug	○ No	○ Yes	○ Don't Remember
Sept-Oct	○ No	○ Yes	○ Don't Remember
Nov-Dec	○ No	○ Yes	○ Don't Remember

R1-8 Does (did) this home have any air cleaning devices? (Examples: air purifier, charcoal filter).

- ○ Yes
- ○ No
- ○ Don't remember

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

R1-9 Is (was) there a gas cooking stove, range or oven in this home?

○ Yes ○ No ○ Don't remember

↓ IF YES:

a. During November through April is (was) this stove/range or oven used to help heat the home?

- ○ Yes
- ○ No
- ○ Don't remember

R1-10 Does (did) this home use any of the following for heating during November through April? (MARK ALL THAT APPLY)

- ○ Regular fireplace
- ○ Wood stove
- ○ Kerosene heater
- ○ Gas from gas company
- ○ Bottled, tank or LP gas
- ○ Don't remember
- ○ Other

R1-11 During the time that you lived in this home, did you take any trips or vacations during the months of May through October that kept you more than 50 miles away from your home for between 1 and 2 months?

○ Yes ○ No ○ Don't remember

↓ IF YES:

a. Record the number of years that you took such trips or vacations.

____ ____ (○ Don't remember)

R1-12 During the time that you lived in this home, did you take any trips or vacations during the months of May through October that kept you more than 50 miles away from your home for more than 2 months?

○ Yes ○ No ○ Don't remember

↓ IF YES:

a. Record the number of years that you took such trips or vacations.

____ ____ (○ Don't remember)

b. Record the longest time that you were away at any one time.

____ MONTHS (○ Don't remember)

SCHOOLS ATTENDED

This section seeks information about all of the schools that you may have attended while you were living at this residence.

PK-0 Were you ever placed in day care, nursery school or pre-kindergarten while you lived at this residence?

○ Yes ○ No ○ Don't remember

→ IF "NO" OR "DON'T REMEMBER", GO TO "ELEMENTARY SCHOOL" SECTION.

↓ IF YES,

a. How many different programs were you in? ____

Day Care/Nursery School/Pre-Kindergarten 1

PK-1 Was this school located within 3 miles of your home?

○ Yes ○ No ○ Don't remember

↓ IF NO/DON'T REMEMBER

a. _____
Street Address

b. _____
City/Town

PK-2 During what years did you attend this school?

____ 19 ____ to ____ 19 ____ (○ Don't remember)
Month Month

PK-3 For how many hours a day did you attend this school?

- ○ Less than 4 hrs.
- ○ 4-8 hrs.
- ○ More than 8 hrs.
- ○ Don't remember

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

Day Care/Nursery School/Pre-Kindergarten 2

PK-1 Was this school located within 3 miles of your home?

○ Yes ○ No ○ Don't remember

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

PK-2 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

PK-3 For how many hours a day did you attend this school?

○ Less than 4 hrs.
○ 4-8 hrs.
○ More than 8 hrs.
○ Don't remember

Day Care/Nursery School/Pre-Kindergarten 3

PK-1 Was this school located within 3 miles of your home?

○ Yes ○ No ○ Don't remember

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

PK-2 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

PK-3 For how many hours a day did you attend this school?

○ Less than 4 hrs.
○ 4-8 hrs.
○ More than 8 hrs.
○ Don't remember

ELEMENTARY SCHOOL

ES-0 How many different elementary schools (Grades K-8) did you attend while you were living at this residence?

____ NUMBER OF SCHOOLS

IF "0", GO TO "HIGH SCHOOL" SECTION.

For each school, please provide the following information:

Elementary School 1

ES-1 What was the name of the school? (Record Don't remember, if appropriate)

Name _____

ES-2 Was this school located within 3 miles of your home?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

ES-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

ES-5 What was the most frequent way that you went to school? (CHOOSE ONLY 1)

○ Walk/bicycle
○ Driven in car
○ School bus
○ Public transporation
○ Don't remember
○ Other

ES-6 How many hours per day were you usually inside the school building?

____ ____ (○ Don't remember)

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

Elementary School 2:

ES-1 What was the name of the school? (Record Don't remember, if appropriate)

Name _____

ES-2 Was this school located within 3 miles of your home?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

ES-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

ES-5 What was the most frequent way that you went to school? (CHOOSE ONLY 1)

○ Walk/bicycle
○ Driven in car
○ School bus
○ Public transportation
○ Don't remember
○ Other

ES-6 How many hours per day were you usually inside the school building?

____ ____ (○ Don't remember)

Elementary School 3

ES-1 What was the name of the school? (Record Don't remember, if appropriate)

Name _____

ES-2 Was this school located within 3 miles of your home?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

ES-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

Elementary School 4

ES-1 What was the name of the school? (Record Don't remember, if appropriate)

Name _____

ES-2 Was this school located within 3 miles of your home?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

ES-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

ES-5 What was the most frequent way that you went to school? (CHOOSE ONLY 1)

○ Walk/bicycle
○ Driven in car
○ School bus
○ Public transportation
○ Don't remember
○ Other

ES-6 How many hours per day were you usually inside the school building?

____ ____ (○ Don't remember)

HIGH SCHOOL

HS-0 How many different high schools (Grades 9-12) did you attend while you were living at this residence?

____ NUMBER OF SCHOOLS

IF "0", GO TO "GENERAL ACTIVITIES" SECTION.

For each school, please provide the following information:

High School 1

HS-1 What was the name of the school?

Name _____

HS-2 Was this school located within 3 miles of your house?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

HS-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

HS-5 Over the years that you attended this school, what was the most frequent way that you went to school?

○ Walk
○ Bicycle/scooter/motorcycle
○ Driven in or drove car
○ School bus
○ Public transportation
○ Don't remember
○ Other

HS-6 What was the usual amount of time that it took to get to school?

_____ _____ MINUTES (○ Don't remember)

HS-7 How many hours a day were you usually inside the school building?

_____ _____ HOURS (○ Don't remember)

HS-8 Did this school have air conditioning?

○ Yes ○ No ○ Don't remember

HS-9 On warm days, were the windows in the classrooms kept open?

○ Yes ○ No ○ Don't remember

HS-10 During air pollution advisories or smog alerts, were the windows kept closed at school?

○ Yes ○ No ○ Never had such advisories/alerts ○ Don't remember

High School 2

HS-1 What was the name of the school?

Name _____

HS-2 Was this school within 3 miles of your house?

○ No ○ Don't remember ○ Yes

↓ IF YES/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

HS-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

HS-5 Over the years that you attended this school, what was the most frequent way that you went to school?

○ Walk
○ Bicycle/scooter/motorcycle
○ Driven in or drove car
○ School bus
○ Public transportation
○ Don't remember
○ Other

HS-6 What was the usual amount of time that it took to get to school?

_____ _____ MINUTES (○ Don't remember)

HS-7 How many hours a day were you usually inside the school building?

_____ _____ (○ Don't remember)

HS-8 Did this school have air conditioning?

○ Yes ○ No ○ Don't remember

HS-9 On warm days, were the windows in the classrooms kept open?

○ Yes ○ No ○ Don't remember

HS-10 During air pollution advisories or smog alerts, were the windows kept closed at school?

○ Yes ○ No ○ Never had such advisories/alerts ○ Don't remember

High School 3

HS-1 What was the name of the school?

Name _____

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

HS-2 Was this school within 3 miles of your house?

○ No ○ Don't remember ○ Yes

↓ IF NO/DON'T REMEMBER

a. _____ Street Address

b. _____ City/Town

HS-3 During what years did you attend this school?

_____ 19 ____ to _____ 19 ____ (○ Don't remember)
Month Month

HS-5 Over the years that you attended this school, what was the most frequent way that you went to school?

○ Walk
○ Bicycle/scooter/motorcycle
○ Driven in or drove car
○ School bus
○ Public transportation
○ Don't remember
○ Other

HS-6 What was the usual amount of time that it took to get to school?

_____ _____ MINUTES (○ Don't remember)

HS-7 How many hours a day were you usually inside the school building?

_____ _____ (○ Don't remember)

HS-8 Did this school have air conditioning?

○ Yes ○ No ○ Don't remember

HS-9 On warm days, were the windows in the classrooms kept open?

○ Yes ○ No ○ Don't remember

HS-10 During air pollution advisories or smog alerts, were the windows kept closed at school?

○ Yes ○ No ○ Never had such advisories/alerts ○ Don't remember

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

GENERAL ACTIVITY PATTERNS

This section seeks information about the amount of time that you typically spend outdoors during the time that you lived at this residence. Please remember to answer each question in relation to the time you lived at this residence only.

OD-1 Compared to others your age, how much time did you typically spend outdoors from May through October?

Age (Yrs)	Did Not Live Here At This Age	Outdoors More Than Most	Outdoors About the Same As Most	Outdoors Less Than Most	Don't Remember
0-2	○	○	○	○	○
3-5	○	○	○	○	○
6-11	○	○	○	○	○
12-17	○	○	○	○	○

OD-2 When you were outdoors during the months of May through October, where were you most likely to be? (Answer for each age period).

Age (Yrs)	Did Not Live Here At This Age	Within 3 Mile of Home	3-5 Miles From Home	More Than 5 Miles From Home	Don't Remember
0-2	○	○	○	○	○
3-5	○	○	○	○	○
6-11	○	○	○	○	○
12-17	○	○	○	○	○

OD-3 During summertime air quality advisories or smog alerts (public announcements concerning high air pollution levels), to what extent did you decrease the time that you spent outdoors? (Answer for each age period.)

Age-Yrs	Did Not Live Here At This Age	Not At All	Lowered By Less Than 50%	Lowered By 50% or more	No Such Advisory	Don't Rem'br
0-2	○	○	○	○	○	○
3-5	○	○	○	○	○	○
6-11	○	○	○	○	○	○
12-17	○	○	○	○	○	○

OD-4 Were you living at this residence during the 12 months prior to coming to the UC Berkeley Campus?

○ Yes ○ No

→ IF NO, SKIP TO "OUTDOOR ACTIVITIES INVENTORY"

↓ IF YES,

a. During this period, how would you compare the amount of time that you spent outdoors during the summer months (May through October), compared to others your own age?

○ More than most
○ About the same as most
○ Less than most
○ Don't remember

b. When you were outdoors during months of May through October of this last year, were you most likely to be...

○ Within 3 miles of home?
○ 3-5 miles from home?
○ 5-20 miles from home?
○ More than 20 miles from home?
○ Don't remember

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

h. During the months of May through October of the last year, what was the average number of times per month that you did these activities?

____ ____ NUMBER [○ Don't Remember]

c. What was the average amount of time that you spent each time you did these activities?

____.____ ____ HOURS.MINUTES

[○ Don't remember]

d. During the months of May through October of this past 12 month period, did you decrease any of these activities during an air pollution advisory or smog alert?

○ Not at all
○ Less than 50%
○ 50% or more
○ Not aware of any such advisories
○ Don't remember

e. Listed below are locations where you may have engaged in one or more of these activities in the months of May through October of this last year.

e(1). Within 3 miles of home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

e(2). At school

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

e(3). More than 3 miles from home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

MODERATE INTENSITY ACTIVITIES

MI-0 While you were living at this residence, did you engage in any of the activities listed under "Moderate Intensity Activities" on the Physical Activity Inventory Page?

○ Yes ○ No

↓ IF YES, → IF NO, SKIP TO "ACTIVITY LIST"

MI-1 Which months of the year did you engage in any of these activities? (Indicate all that apply).

○ January ○ July ○ Don't remember
○ February ○ August
○ March ○ September
○ April ○ October
○ May ○ November
○ June ○ December

MI-2 When you engaged in one or more of these activities, what was the average number of times per month that you did these activities?

____ ____ NUMBER [○ Don't remember]

a. In what months did you do any of these activities most frequently? (Indicate all that apply).

○ January-February ○ July-August
○ March-April ○ September-October
○ May-June ○ November-December

MI-3 What was the average amount of time that you spent each time you did the most frequent of these activities May through October?

____.____ ____ (HOURS.MINUTES) [○ Don't remember]

MI-4 For how many years did you engage at least in one of these activities while you were living at this residence?

____ ____ NUMBER OF YEARS [○ Don't remember]

MI-5 If an air pollution advisory or smog alert was issued, how much did you reduce your participation in one of these activities?

○ Not at all
○ Less than 50%
○ 50% or more
○ Never heard about such advisories/alerts
○ Don't remember

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

OUTDOOR ACTIVITIES

This section seeks information on the kinds of outdoor activities in which you engaged while you were living at this residence. Please remember to answer each question in relation to this residence only.

Refer to "Physical Activity Inventory" page as needed for this section.

HEAVY INTENSITY ACTIVITIES

HI-0 While you were living at this residence, did you engage in any of the activities listed under "Heavy Intensity Activities" on the Physical Activity Inventory Page?

○ Yes ○ No

↓ IF YES, → IF NO, SKIP TO "MODERATE INTENSITY ACTIVITY"

HI-1 Which months of the year did you engage in any of these activities? (Indicate all that apply).

○ January ○ July ○ Don't Remember
○ February ○ August
○ March ○ September
○ April ○ October
○ May ○ November
○ June ○ December

HI-2 When you engaged in one or more of these activities, what was the average number of times per month that you did these activities?

____ ____ NUMBER [○ Don't remember]

a. In what months did you do any of the activities most frequently? (Indicate all that apply).

○ January-February ○ July-August
○ March-April ○ September-October
○ May-June ○ November-December

HI-3 What was the average amount of time that you spent each time you did these activities from May through October?

____.____ ____ (HOURS.MINUTES) [○ Don't Remember]

HI-4 For how many years did you engage at least in one of these activities while you were living at this residence?

____ ____ NUMBER OF YEARS [○ Don't Remember]

HI-5 If an air pollution advisory or smog alert was issued, how much did you reduce your participation in one of these activities?

○ Not at all
○ Less than 50%
○ 50% or more
○ Never heard about such advisories/alerts
○ Don't remember

HI-6 Listed below are locations where you may have engaged in one or more of these activities. For each location, indicate how frequently you engaged in activities in this category at the particular location.

a. Within 3 miles of home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

b. At school

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

c. More than 3 miles from home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

HI-7 Were you living at this residence during the 12 months prior to coming to the UC Berkeley campus?

○ Yes ○ No

→ IF NO, SKIP TO "MODERATE INTENSITY ACTIVITY"

↓ IF YES,

a. During these 12 months, did you engage in any of these "Heavy Intensity Activities" during... (INDICATE ALL THAT APPLY)

○ May-June
○ July-August
○ September-October
○ Did not engage in any of these activities in these months → SKIP TO "MODERATE INTENSITY ACTIVITIES"

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

MI-6 Listed below are locations where you may have engaged in one or more of these activities. For each location, indicate how frequently you engaged in activities in this category at the particular location.

a. Within 3 miles of home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

b. At school

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

c. More than 3 miles from home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

MI-7 Were you living at this residence during the 12 months prior to coming to the UC Berkeley campus?

○ Yes ○ No

→ IF NO, SKIP TO "DRIVING SECTION"

↓ IF YES,

a. During these 12 months, did you engage in any of these "Moderate Intensity Activities" during... (INDICATE ALL THAT APPLY)

○ May-June?
○ July-August?
○ September-October?
○ Did not engage in any of these activities in these months → SKIP TO "DETAILED ACTIVITY LIST"

b. During the months of May through October of the last year, what was the average number of times per month that you did the most frequent of these activities?

____ ____ NUMBER [○ Don't remember]

c. What was the average amount of time that you spent each time you did the most frequent of these activities?

____.____ ____ HOURS.MINUTES

[○ Don't remember]

d. During the months of May through October of this past 12 month period, did you decrease any of these activities during an air pollution advisory or smog alert?

○ Not at all
○ Less than 50%
○ 50% or more
○ Not aware of any such advisories
○ Don't remember

e. Listed below are locations where you may have engaged in one or more of these activities in the months of May through October of this last year.

e(1). Within 3 miles of home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

e(2). At school

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

e(3). More than 3 miles from home

○ 50% or more of the time
○ Less than 50% of the time
○ Not at all
○ Don't remember

GO TO "DETAILED ACTIVITY LIST"

DETAILED ACTIVITY LIST

PLEASE LIST ALL OF THE PHYSICAL ACTIVITIES IN WHICH YOU ENGAGED DURING THE TIME THAT YOU LIVED AT THIS RESIDENCE

fill in the information requested for each activity that you list

OUTDOOR ACTIVITY ONLY

activity	months of the year that you perform this activity (*check each that applies*)	average times per month done May thru October	average amount of time per session	number years done in relation to this residence (*nearest half yr*)	where activity performed in relationship to residence: within 5 miles of home (*1=Usually, 2=Sometimes, 3=Never, 4=Don't Remember*) (CIRCLE CHOICE IN EACH COLUMN)	more than 5 miles from home	at school
1	jan feb mar apr may jun jul aug sep oct nov dec		hr min		1---2---3---4	1---2---3---4	1---2---3---4
2			hr min		1---2---3---4	1---2---3---4	1---2---3---4
3			hr min		1---2---3---4	1---2---3---4	1---2---3---4
4			hr min		1---2---3---4	1---2---3---4	1---2---3---4
5			hr min		1---2---3---4	1---2---3---4	1---2---3---4
6			hr min		1---2---3---4	1---2---3---4	1---2---3---4
7			hr min		1---2---3---4	1---2---3---4	1---2---3---4
8			hr min		1---2---3---4	1---2---3---4	1---2---3---4

WHEN YOU HAVE COMPLETED THIS LIST, GO TO THE SECTION LABELLED "DRIVING".

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

WH-3 For how many years did you have a job in which you worked outdoors at least part of the time during the months of May through October?

____ ____ NUMBER OF YEARS

[01 - 1; 02 - 2; ○ Don't remember]

For each outdoor job in the months of May through October, provide the following information (start with most recent summer during which you lived at this residence).

Job 1

J1-1 In what year did you have this job?

19____ ____ [○ Don't remember]

J1-2 Distance of job from residence:

- ○ In my neighborhood
- ○ 1-3 miles
- ○ 4-10 miles
- ○ More than 10 miles

a. Location of job: (Put "Don't Remember" where applicable).

Street

City/Town Zip Code

State (If not California)

J1-3 Amount of time each work day spent outdoors:

- ○ A full work day (8 or more hours per day)
- ○ At least half a work day
- ○ Less than half a workday

J1-4 Number of days worked each week:

____ DAYS [○ Don't remember]

J1-5 Months in which you worked. (Mark all that apply).

	All Weeks	2-3 Weeks	1 Week Or Less	Did Not Work
May	○	○	○	○
June	○	○	○	○
July	○	○	○	○
August	○	○	○	○
September	○	○	○	○
October	○	○	○	○

J1-6 Did this job involve heavy physical labor or participation in heavy athletic activities?

○ Yes ○ No

↓ IF YES:

- ○ Never or rarely
- ○ Sometimes
- ○ Most of the time
- ○ Always
- ○ Don't remember

J1-7 Did this job involve working on or alongside a freeway or other heavily travelled main thoroughfare?

○ Yes ○ No

↓ IF YES:

- ○ Never or rarely
- ○ Sometimes
- ○ Most of the time
- ○ Always
- ○ Don't remember

→ IF THIS WAS THE LAST JOB AT THIS RESIDENCE AND IF THIS WAS THE LAST RESIDENCE THAT YOU LISTED, YOU ARE FINISHED. IF NOT, GO TO THE NEXT RESIDENCE HISTORY FORM.

THANK YOU.

Job 2

J1-1 In what year did you have this job?

19____ ____ [○ Don't remember]

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

J1-2 Distance of job from residence:

- ○ In my neighborhood
- ○ 1-3 miles
- ○ 4-10 miles
- ○ More than 10 miles

a. Location of job: (Put "Don't remember" where applicable).

Street

City/Town Zip Code

State (If not California)

J1-3 Amount of time each work day spent outdoors:

- ○ A full work day (8 or more hours per day)
- ○ At least half a work day
- ○ Less than half a workday

J1-4 Number of days worked each week:

____ DAYS [○ Don't remember]

J1-5 Months in which you worked. (Mark all that apply).

	All Weeks	2-3 Weeks	1 Week or Less	Did Not Work
May	○	○	○	○
June	○	○	○	○
July	○	○	○	○
August	○	○	○	○
September	○	○	○	○
October	○	○	○	○

J1-6 Did this job involve heavy physical labor or participation in heavy athletic activities?

○ Yes ○ No

↓ IF YES:

- ○ Never or rarely
- ○ Sometimes
- ○ Most of the time
- ○ Always
- ○ Don't remember

J1-7 Did this job involve working on or alongside a freeway or other heavily travelled main thoroughfare?

○ Yes ○ No

↓ IF YES:

- ○ Never or rarely
- ○ Sometimes
- ○ Most of the time
- ○ Always
- ○ Don't remember

→ IF THIS WAS THE LAST JOB AT THIS RESIDENCE AND IF THIS WAS THE LAST RESIDENCE THAT YOU LISTED, YOU ARE FINISHED. IF NOT, GO TO THE NEXT RESIDENCE HISTORY FORM.

THANK YOU.

Job 3

J1-1 In what year did you have this job?

19____ ____ [○ Don't remember]

J1-2 Distance of job from residence:

- ○ In my neighborhood
- ○ 1-3 miles
- ○ 4-10 miles
- ○ More than 10 miles

a. Location of job: (Put "Don't remember" where applicable).

Street

City/Town Zip Code

State (If not California)

J1-3 Amount of time each work day spent outdoors:

- ○ A full work day (8 or more hours per day)
- ○ At least half a work day
- ○ Less than half a workday

J1-4 Number of days worked each week:

____ DAYS [○ Don't remember]

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

DRIVING

This section seeks information about time that you spent in motor vehicles, other than going to and from school, during the time that you lived at this residence.

D-1 During the time that you lived at this residence, how often did you drive in the following types of vehicles during the months May through October? (Include time as passenger or driver).

	Never	Daily	Weekly But Not Daily	Monthly, But Not Weekly	Less Than Once Per Month	Don't Remember
Car: Fixed Roof/ Windows Open	○	○	○	○	○	○
Car: Convertible or Open Sunroof	○	○	○	○	○	○
Car: w/air conditioning on	○	○	○	○	○	○
Motorcycle	○	○	○	○	○	○
Motor Scooter	○	○	○	○	○	○
Bicycle	○	○	○	○	○	○

D-2 During the time that you lived at this residence, how often did you drive in the following locations during the months May through October? (Include times as passenger and/or driver).

	Never	Daily	Wkly But Not Daily	Monthly, But Not Wkly	Less Than Once P/Mo.	Don't Remember
Freeways w/o traffic congestion	○	○	○	○	○	○
Freeways w/traffic congestion	○	○	○	○	○	○
City/Town streets w/o traffic congestion	○	○	○	○	○	○
City/Town streets w/traffic congestion	○	○	○	○	○	○
Country or Rural Roads	○	○	○	○	○	○

WORK HISTORY

WH-1 During the years that you lived at this residence, did you have any part-time or summer jobs?

○ Yes ○ No

→ IF "NO", AND THIS WAS THE LAST RESIDENCE THAT YOU LISTED, YOU ARE FINISHED. IF NOT, GO TO THE NEXT RESIDENCE HISTORY FORM.

THANK YOU.

WH-2 Did any of these jobs involve working outdoors in the summer months (May through October)?

○ Yes ○ No

→ IF "NO", AND THIS WAS THE LAST RESIDENCE THAT YOU LISTED, YOU ARE FINISHED. IF NOT, GO TO THE NEXT RESIDENCE HISTORY FORM.

THANK YOU.

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

J1-5 Months in which you worked. (Mark all that apply).

	All Weeks	2-3 Weeks	1 Week or Less	Did Not Work
May	o	o	o	o
June	o	o	o	o
July	o	o	o	o
August	o	o	o	o
September	o	o	o	o
October	o	o	o	o

J1-6 Did this job involve heavy physical labor or participation in heavy athletic activities?

o Yes o No

↓ IF YES:
o Never or rarely
o Sometimes
o Most of the time
o Always
o Don't remember

J1-7 Did this job involve working on or alongside a freeway or other heavily travelled main thoroughfare?

o Yes o No

↓ IF YES:
o Never or rarely
o Sometimes
o Most of the time
o Always
o Don't remember

If this was the last residence that you listed, you are finished. If it is not the last residence, move to the next residence form. Thank you.

RESPIRATORY HEALTH EFFECTS OF CHRONIC AMBIENT OZONE EXPOSURES
MAIN QUESTIONNAIRE

PHYSICAL ACTIVITY INVENTORY

Listed below is a series of activities in which you may have participated while you were living at this residence. This list should be used to answer questions HI-0 → HI-7 and MI-0 → MI-7. Answer "yes" only if the activities were performed OUTSIDE. Include personal leisure time activities, activities performed on school teams or as part of any other organized athletic program or as part of group to which you may have belonged. If you are unsure of an answer or don't remember, choose the code for "Don't Remember" provided in each column. THE LISTS PROVIDE EXAMPLES OF TYPES OF ACTIVITIES FOR LEVELS OF INTENSITY; YOU MAY INCLUDE OTHER ACTIVITIES THAT ARE NOT LISTED.

HEAVY INTENSITY ACTIVITIES
Jogging or running
Tennis (singles or doubles) or badminton
Squash
Handball
Bicycling faster than 10 mph (15km/hr).
Bicycling hard on an exercise bike
Swimming
Weight lifting (outdoors)
Basketball (on a team or in games)
Football (touch or contact)
Rollerblade or ice skating (outdoors)
Workout at gym or health club (outdoors)
Soccer
Calisthenics/Aerobics (outdoors)
Gymnastics (outdoors)

MODERATE INTENSITY ACTIVITIES
Baseball, Softball
Volleyball
Golf (walking and carrying clubs)
Home exercise or calisthenics
Leisurely jogging or brisk walking
Bicycling (leisurely (less than 10 mph)
Drill Team

FINAL QUESTION, LAST RESIDENCY PRIOR TO COMING TO UC BERKELEY

Think about a usual **summer day** (May through October) during the summer prior to coming to UC Berkeley campus. On average, how many hours per day did you engage in the following types of activity? In total, your answers should add up to 24 hours for a usual working day (= first column) and 24 hours for a usual day on weekends (= second column).

Type of activity	location	Please, fill in these two columns ↓ hours/minutes per day on working day (hh : mm)	weekend day (hh : mm)
A) HEAVY PHYSICAL ACTIVITIES i.e. you sweat / are exhausted, e.g. jogging, strenuous sports, biking uphill, strenuous gardening or jobs (mason, carpenter, plumber, construction works etc.	outdoors	___ : ___	___ : ___
	indoors (= in buildings)	___ : ___	___ : ___
B) MODERATE PHYSICAL ACTIVITIES e.g.: housekeeping, moderate sport activities, walking, hiking, light gardening, biking on level surface, job activities not in sitting position etc.	outdoors	___ : ___	___ : ___
	indoors (= in buildings)	___ : ___	___ : ___
C) LIGHT PHYSICAL ACTIVITIES e.g.: sitting, office work, driving / commuting, making phone calls, self care etc.	outdoors	___ : ___	___ : ___
	indoors	___ : ___	___ : ___
D) REST / SLEEP	outdoors	___ : ___	___ : ___
	indoors (= in buildings)	___ : ___	___ : ___
	TOTAL :	24 hours	24 hours

YOUR NAME: ..... DATE: .....
first last

HENEXTRAQU1.DOC

PFT ELIGIBILITY

NAME: _____ AGE: _____
DATE: _____ TIME: _____
GENDER: _____ HEIGHT: _____ CM.

Please Circle Choice

1. Do you currently have a runny or stuffed nose? Y N
2. Do you currently have a cough? Y N
3. Are you currently experiencing wheezing/whistling in your chest? Y N
4. In the past 72 hours, have you had a fever or felt like you might be getting a fever? Y N
5. In the past 72 hours, have you had muscle aches or felt like you might be getting a cold or the flu? Y N
6. Have you had a cold or flu in the last 7 days? Y N

   IF "YES" TO QUESTION 6, ANSWER 6A:

   6a. Did you seek medical care? Y N

   IF "YES" TO QUESTION 6A, ANSWER 6B:

   6b. Was an inhaler prescribed? Y N
7. Do you drink caffeinated beverages (coffee, tea, cocoa, soda)? Y N

IF "YES": What time did you last have a drink of any of the following. (Answer for all that apply).

	TIME	AM/PM
COFFEE	_____	____
TEA	_____	____
COCOA	_____	____
SODA	_____	____

SPIROMETRY

INTRODUCTION:

The principle test of lung function that will be used for SPPARCS is known as "spirometery" (named after the instrument used to make the measurement--a "spirometer") or the "forced vital capacity maneuver". The basic principal behind the test is to have a subject fill his/her lungs with as much air as s/he can and then to rapidly, and forcefully, exhale the air until s/he feels that no more air is left in their lungs. The spirometer records the amount of air that is blown out and the amount of time that it takes. From this formation a number of measurements can be made about the mechanical function of the person's lung.

A high level of subject cooperation is required to obtain results from this test. Failure to obtain a maximum effort with each test and/or lack of attention to other details that affect the test will lead to results that are not accurate or reproducible.

I. Measurements that will be made:

1. forced expiratory volume in the first second (**FEV_1**): measures the amount of air that the subject can exhale in the first second of forced exhalation; this measurement is a very strong predictor of all-cause mortality in older individuals

   a. this measurement is affected adversely if the subject starts the maneuver too slowly and doesn't blow as hard as s/he can right from the start

2. forced vital capacity (**FVC**): measures the total amount of air that a subject can exhale after taking a full inspiration and then forcibly emptying the lung until no more air is left

   a. this measurement is affected adversely if the subject does not empty his/her lungs as completely as possible and by how hard they blow; paradoxically, the slower the subject blows, the larger the result will be (this is not what is desireable).

3. flows at specific lung volumes

   a. peak expiratory flow rate (**PEFR**): highes airflow rate obtained during the test (also being measured in the subjects' homes by the mini Wright peak flow meters

   b. flows at specific lung volumes, especially flows after the subject has exhaled the first 40% of the amount of air in their lungs ($Vmax_x$--where "$_x$" is the volume at which the flow is measured:

   these measurements are of particular importance, since they do not depend upon the subject's effort but rather on the intrinsic mechanical properties of the lung

II. Preliminary preparation

A. Before beginning each subject, use the stamps provided to stamp the chart paper (see Part 5 for an example). Fill in the identifying information on the top of the chart paper.

B. Place the chart paper on the drum and trace a baseline on the paper by turning on the drum for one complete revolution. It is helpful to start this int he same place for each subject, namely at the point of the overlap of the chart paper.

C. Position the pen for the first test just past the point of overlap. For each succeeding test, start the curve about 1 inch further in.

D. Have the subject insert a mouthpiece into the spirometer hose, and give the subject the noseclip which should be used during the forced expiration maneuver.

E. The tester should have a spare mouthpiece in hand to demonstrate the technique of performing the forced expiratory maneuver, if necessary.

III. Testing the subject

A. Start by giving a simple, but full explanation to the subject of what the forced expiratory maneuver involves, as follows:

1. "Please sit comfortably with both feet on the floor and, whenever you are ready, take as deep a breath as you can, place your mouth around the mouthpiece with your lips tightly sealed, and then breathe out as hard, as fast and as long as you can. Keep breathing out until I tell you to stop."

a. at this point, wait until the subject is ready, and start the drum just before the person begins the forced expiration. Failure to start the drum at the right moment may result in a curve that is not acceptable.

b. observe the subject carefully during the expiration to make sure that he/she has fully understood the instructions and is performing the forced expiration adequately.

APPENDIX B. Manufacturer's Documentation of Pulmonary Function Instrument

Performance characteristics of the SensorMedics mass flow sensor are presented; and calibration procedures for obtaining MEFV and SBNW curves are described. This appendix may be obtained by writing the Health Effects Institute, 955 Massachusetts Avenue, Cambridge, MA 02139 or sending your request via e-mail to pubs@healtheffects.org. Please provide the first author's name, the Investigators' Report title, and the title of the appendix.

APPENDIX C. Pulmonary Function Measurement Protocols and Quality Control Procedures

Instructions and quality control requirements are presented for performance of the MEFV maneuver and SBNW test as well as instructions for the performance of height and weight measurements. Examples of SBNW curves and accompanying flow curves are provided to illustrate application of the criteria.

c. encourage the subject to keep pushing air out of the lungs throughout the entire forced expiration, for example, tell the subject to "keep going, keep pushing".

d. stop the drum and instruct the subject to stop blowing when the tracing reaches a plateau for about 1 to 2 seconds - note that usually this happens after about 6 seconds, and the six second line is marked on the side of the base below the drum (when the start of the curve passes this line 6 seconds has elapsed).

e. mark the curve at several points with a pencil by recording the number of the tracing (ie., the first attempt is the first tracing, etc.) directly on the curve at the beginning and at the end, and by drawing a line which touches the tracing (put the tracing number at the end of this line) anywhere along the tracing where it should be marked. It should be marked at the maximal point if the tracing reaches a peak and then starts to decline, as these points will be hard to discern once the rest of the tracings are made. It should also be marked where something unusual occurs and a note made right on the chart paper. Please hold the chart paper tightly while marking on it, as it is very important not to move it around between tracings.

B. Continue by having the subject perform a second attempt, judging through examination of the curves whether the subject is performing the expiration correctly. Additional instruction may be needed and this can only be judged by observing the participant and the curves produced. Once the person fully understands what is expected, the curves should all provide very similar measurements of FEV1 and FVC. Additional instructions which may be needed include the following:

1. "Fill your lungs fully, then stop a moment, bring the tube up to your mouth and breathe out as fast as you can"

2. "Keep the tube away from your mouth while you are breathing in"

3. "Put the tube between your teeth and seal your mouth around the mouthpiece"

4. "Blow out as if you are saying the word 'haaa'"

5. "Try to keep going until I tell you to stop, and keep blowing out for the whole time"

6. a demonstration by the tester of what the maneuver involves, using a mouthpiece held in the hand (not necessary to connect it to the tubing for the purpose of demonstration

C. Continue to test the subject, until a maximum of 8 tracings have been attempted. The minimum number of attempts is 5, and after that you may stop when 3 acceptable tracings have been made and there is good reproducibility (please see below for a definition of acceptable tracings).

D. Check the curves for acceptability and reproducibility while the paper is on the drum. When you judge that the subject is finished, take the paper off the drum, record the spirometer temperature and check the curves for acceptability and reproducibility again. If there is any question about whether 3 curves are acceptable, you may put the paper back on carefully (make sure the pen is on the same baseline) and have the subject perform another forced expiration if necessary, as long as the total number of maneuvers does not exceed 8.

E. Do a quick calculation of FEV1 and FVC, choosing the maximal values and compute the ration of FEV1/FVC which will be reported to the subject as a percentage value (there will be a sheet for recording this value for the subject's information). Please see Part 5. for instructions for measurements.

IV. Determining acceptability of the tracings:

A. FVC: determining the end of the test

1. an obvious plateau in the curve resulting in no change in volume for approximately 1 to 2 seconds (a volume decrease is, for the purposes of end of test selection, equivalent to no change in volume), with an exhalation of at least 6 seconds (longer times are often required in persons with obstruction)

a. note, no change in volume means volume stays within ± 40 cu cm.

2. or, a forced exhalation of reasonable duration (maximum 15 seconds)

3. or, when the subject cannot, for legitimate reasons, continue further exhalation

B. FVC: determining a satisfactory start of test

1. to achieve accurate 'time zero' (ie., the starting point of curve for measurement purposes) and to ensure that the FEV1 comes from a maximal effort curve, the extrapolated volume should be less than 5% of the FVC or 100 cu cm, whichever is greater (see Part 5. example of a late start with a tangent line drawn to determine time zero and extrapolated volume).

a. note that generally this means that if the curve starts with a straight vertical line. this line must be less than approx. 1/4 inch

C. FVC: determining whether the curve is acceptable, given that the start and end of the test are acceptable:

1. the tester should observe that the subject understood the instructions and performed the maneuver with a maximum inspiration, with a good start, with a smooth continuous exhalation, with maximal effort, and <u>without</u> any of the following problems (see attached curves in Part 5):

a. coughing during the first second of the maneuver, or any other cough that, in the tester's judgement, interferes with measurement of accurate results

b. valsalva maneuver (glottis closure)

c. early termination of expiration (in most subjects this would be exhalation of less than 6 seconds)

d. a leak

e. an obstructed mouthpiece, eg., obstruction due to the tongue being placed in front of the mouthpiece

V. Determining reproducibility of the tracings

These criteria are used in deciding whether the subject should perform more than the minimum of 5 forced expirations (maximum is 8). Please note the acceptability criteria should be applied before the reproducibility criteria are even considered (ie., first make sure you have acceptable tracings, and then determine if the subject needs to do more than 5 maneuvers by examining the reproducibility of the tracings). Please see the attached flow chart for a graphical representation of these steps.

A. Reproducibility criteria:

1. The largest FVC and the second largest FVC should not vary by more than 5% of the largest reading or 0.100 L, whichever is greater.

2. The largest FEV1 and the second largest FEV1 should not vary by more than 5% of the largest reading or 0.100 L, whichever is greater.

FIVE PERCENT OF FVC AND FEV1 VALUES

VALUE (LITERS)	5% OF VALUE (CU CM)
2.0	100
2.5	125
3.0	150
3.5	175
4.0	200
4.5	225
5.0	250
5.5	275
6.0	300

PROTOCOL FOR SINGLE BREATH NITROGEN WASHOUT

The Single Breath Nitrogen Washout Test (SBNWT) is to be performed after the completion of the maximum forced expiratory flow-volume (MEFV) maneuvers. Before proceeding to the SBNWT, ask the subject if s/he would like to rest before continuing. If the subject wishes to rest, allow 3-5 minutes; and then proceed.

I. CALIBRATION:

A. The calibration of the N_2 analyzer is to be carried out at the start of each work day in accordance with the procedures provided in Section 10.2 of the 2100 System Operator's Manual.

1. If the equipment remains on for the entire day, no further calibration is required.
2. If the equipment is turned off at any time during, recalibration is required prior to the performance of any further testing.

B. 1. The results of each calibration are to be recorded in the calibration log book as follows:

2. date, time, "successful", value of N_2 analyzer between 75-80, N_2% after analyzer is zeroed
3. if the calibration is not successful, indicate the problem and the steps taken to correct it (this always must include a discussion with the technical rep from SensorMedics--name of individual to be recorded along with date and time of conversations--NO TESTING IS TO BE CARRIED OUT UNTIL A SATISFACTORY CALIBRATION HAS BEEN ACHIEVED

II. CRITERIA FOR ACCEPTABLE TESTS: (modified from those provided by Division of Lung Diseases, NHLBI: Suggested Standardized Procedures for Closing Volume Determinations (Nitrogen Method). July, 1973)

A. **All** of following criteria must be met for a curve to be acceptable--each curve is to be printed and the printout evaluated to determine acceptability criteria--DO NOT USE THE CURVE ON THE CRT FOR THIS PURPOSE.

1. mean expiratory flow after the first 500 ml is expired must be within 300-600 ml/sec as indicated on the display
   a. except for the first 500 ml of expiration, expiratory flow transients may not exceed the 600 ml/sec line for a volume of 300 ml
      (1) except for the first 500 ml of expiration, expiratory flow may exceed 600 ml/sec on only 1 occasion, if the volume over which the transient occurs is less than 300 ml
         (a) the volume subsumed by the flow transient is measured as the width of the transient at the level of the *.6L/sec* line on the flow trace
   b. no specific criteria are available for flows that fall below 300 ml/sec after the first 500 ml of volume has been expired
      (1) for our purposes, a test will be acceptable provided that there are no more than 2 flow transients of less than 300 ml/sec over a volume of 300 ml and no more than a total of 3 transients
         (a) the volume subsumed by the flow transient is measured as the width of the transient at the level of the *.3L/sec* line on the flow trace
         (b) do not count as flow transients any flows below .3L/sec that occur after $\geq$75% of FVC has been expired or after the closing volume point occurs
2. the expired VC must be not less than 5% of the best FVC obtained during the MEFV maneuvers
   (a) each VC must be within 10% of the best FVC obtained during the SBNWT
3. there must not be a "step" change in expired N_2 concentration with continued cardiogenic oscillations

III. PERFORMANCE OF THE TEST:

A. Three acceptable tracings, with a maximum of 8 attempts (not including practice), are to be obtained from each subject. If the first 3 tests are acceptable **and** reproducible, you do not have to go on.

1. all subjects are to be given at least 1 practice attempt at the start of the testing (a second practice attempt, prior to the start of testing, is permitted at the discretion of the technician)
   a. the data from this attempt is NOT to be saved even if it is an acceptable test
   b. this practice attempt is NOT counted as 1 of the 8 attempts
2. the test is performed in a sitting position and with a noseclip
3. be sure that you use the small mouthpiece required by the small rubber adapter

B. Explain and demonstrate the details of the test: (instructions for posture and placement of the mouthpiece are the same as those used for the MEFV maneuver

1. Several points are important to stress in the verbal explanation and the demonstration:
   a. when emptying his/her lungs, the subject needs to empty as completely as possible and does not have to do so rapidly
      (1) use phases such as "until you feel like you have absolutely no more air in your lungs"; until you feel that you can't possibly get any more air out of your lungs"; "you don't have to hurry"
   b. when filling his/her lungs, the subjects needs to do so smoothly and completely and does not have to hurry
      (1) use phrase such as those that you use to get to TLC for the MEFV maneuvers
   c. it is critical that the subject understand that the successful completion of the test depends upon their ability to exhale at a slow, controlled rate
      (1) during your explanation, show the subject the flow graph with its dotted lines at 300 ml/sec and 600 ml/sec and explain that s/he is to watch this graph throughout the test and to keep the moving line (the subjects actual air flow rate) between the 2 dotted lines at all times
      (2) after you have completed your demonstration, show the subject your flow curve to reiterate this point
      (3) after the subject has completed his/her practice curve, review their flow curve with him/her to identify problems or to provide positive feedback
      (4) during the performance of the maneuver, you should be monitoring the flow curve and be using such phases as: "remember to keep the your line between the dotted lines"; "try not to let your line go above the top dotted line at any time"; "good job, keep going"; "that's nice and smooth, keep it up"
   d. emphasize that the subject will be expected to empty his/her lungs as completely as possible, just as s/he did during the MEFV maneuver; use such phrases as: "until you feel that you have no more air left in your lungs"; "until your lungs are completely empty"
      (1) as the subject nears the end of each test (indicated by a clear increase in the N_2 concentration or a more marked increase in the rate of increase), use such phrases as: "keep pushing"; "push it out, push it out"; "keep going"
         (a) you should compute the subject's target VC (see Section IIA2 above) for each test so that you know when the subject has reach an acceptable VC--keep encouraging the subject to reach the volume that you are expecting
            i) when the desired has been achieved, the subject can stop

C. Before beginning the testing with the subject, position the subject so that s/he clearly can see the CRT

D. Follow the directions in Section 10.3 of the Operator's Manual for the operation of the equipment during the testing

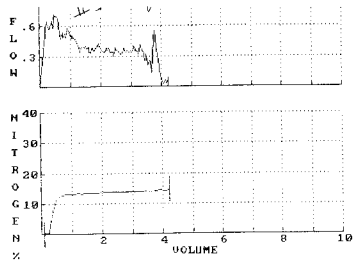
1. be sure that you activate the *F1* key or the hand-held buttom before the subject has reached a full exhalation--**failure to do so will result in incomplete delivery of the O_2 bolus and falsely elevated N_2 concentrations**
   a. activation of the key (button) at the beginning the exhalation flow plateau (determined from tracing on monitor) will assure proper delivery of the O_2 bolus

E. After each test is performed:

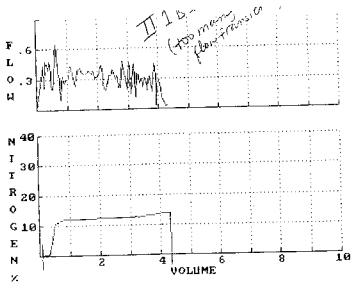
1. place the right-most vertical cursor as far to the right as it will go (the cursor should overlap the vertical line at the end of the N_2 curve)--no closing volume will be measured by the computer as a result of this
   a. print the curve at this point and evaluate the test according to the criteria given in Section IIA above--
      (1) if the curve is acceptable, save the results in the computer
      (2) save the printout for all tests, including those that are not acceptable
      (3) write the trial number on the printout
      (4) for the curves that are not acceptable, also write the criterion/criteria was/that were not met (use the number[letter](number) that corresponds to the appropriate criterion/criteria in Section IIA
   b. after, the subject has left the lab, the closing volume point will be determined from the printed curved according to the following as modified from Craven N, et al. (Computer analysis of the single-breath nitrogen washout curve. Am Rev Respir Dis 1976;445-9.)
      (1) use the calipers to measure the height of the largest cardiogenic oscillation as determined by your visual inspection (should be $\geq$ 0.3% N_2)
         (a) if no cardiogenic oscillation is $\geq$0.3% N_2, use the criterion given in *(4)* below
         (b) if the largest cardiogenic oscillation is $\geq$3 times greater than the next largest, use the next largest for the measurement
      (2) place the small lucite ruler over the phase III of the N_2 washout curve such that the rule overlays phase III between the 750-1750 ml volume points

(3) the CV point is that point where phase III (after the 1750 ml volume point) departs by > 3 times the magnitude of the cardiogenic oscillation that was measured

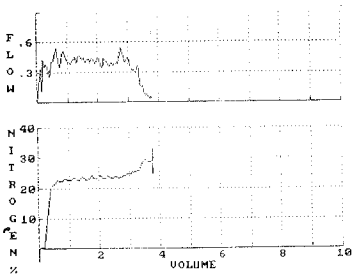
(4) if no such departure is observed (as will be common in the age group that we are studying) or if the height of the cardiogenic oscillations could not be measured, the CV point is that point after the 1750 ml point where the positive deviation is maintained over more than 10% of VC



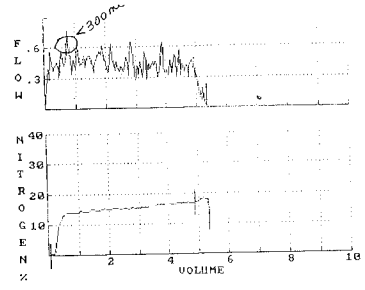
NOT ACCEPTABLE--did not reach desired flow range within first 500ml of expiration



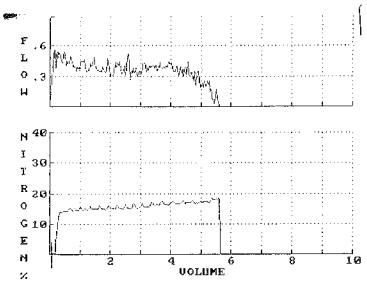
NOT ACCEPTABLE--too many flow transients below 300ml/sec



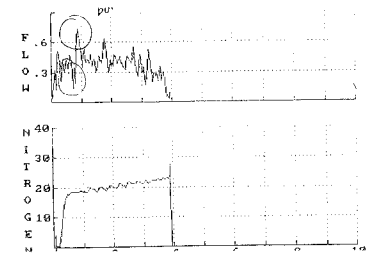
"IDEAL CURVE SHOWN TO ALL SUBJECTS WHEN TEST EXPLAINED AND WHENEVER SUBJECT HAVING PERFORMANCE PROBLEMS



ACCEPTABLE--single flow transient < 300ml



ACCEPTABLE CURVE, NO CLOSING VOLUME POINT PRESENT



ACCEPTABLE--flow transients both <300ml; only 1 transient above and below range

ANTHROPOMETRIC MEASUREMENTS

(Lohman, 1988 #111)

I. **Introduction**

The term "anthropometric measurements" refers to measurements of body size and shape. The **SPPARCS** Project will be making a number of these measurements during the home visit and in the laboratory. Some measurements will made both at the home and laboratory visits and some only in the home. The measurements that will be made are: height, weight, selected skinfold thicknesses and body circumferences. The measurements of skinfold thickness and body circumferences are being obtained to estimate body fat distribution and indirectly to estimate lean body (muscle and bone) mass. These latter measures are important in our analysis of the laboratory exercise testing.

It is essential that each set of directions be followed **exactly** as written. We must assure that the measurements that we obtain are accurate and uninfluenced by who actually made the measurement. To assure that your performance of the protocols does not change over time, you will undergo periodic testing by the Project Director or one of the Project investigators.

Each subject has been instructed to dress in such a manner that it will be feasible for you to make the measurements. If subjects are not properly dressed for a given measurement or set of measurements, do not try to make them until the subject has changed into the proper clothing. If the subject does not want to change, make only those measurement for which the clothing is appropriate.

II. **Performance Of The Tests**

A. Weight

1. Procedure

a. The subject should be in stocking feet. Both feet should be on the scale completely. The subject's hands should hang loosely at his/her side, and the subject should be standing straight.

(1) If the subject cannot stand without support, do not try to weigh the subject. For these latter subjects, ask them their weight, and record their answer in the appropriate spaces on the coding sheet.

2. Equipment

a. The scale should be placed on a hard floor. Do not make the measurement on a carpeted floor.

(1) To activate the scale, press the scale with your foot on the red hexagon. The press should be firm and quick. First and "888.8" will appear, followed by a "000.0".

(2) When the "000.0" appears, have the subject step on the scale as directed above. When the weight appears on the scale and does not change, record the result before the subject gets off the scale.

(3) Record the weight to the nearest pound (.1 to .4, round down; .5 to .9, round up).

The electronic scales should be protected from trauma. If the scale becomes soiled, the surface can be wiped with a damp cloth.

B. Height

1. Home Visit: Procedure

a. Find a wall that is unobstructed by pictures, furniture, etc. and that comes down to a non-carpeted floor. Open the carpenter's ruler to at least 6'6", and hold it against the wall.

b. Have the subject in stocking feet.

c. Have the subject step back against the wall. The subject's arms should hang freely against the trunk, with palms facing the thighs. The subject's heels should be touching each other and the base of the wall. The feet should make an angle of about 60° with each other. The subject's head, shoulder blades and the buttocks also should touch the wall. If the subject is unable to have his/her head, shoulder blades and buttocks touch the wall, position the subject so that the buttock and heels or the buttocks and head are touching the wall. The subject's head should be placed such that the eye sockets and the opening of the ears form a line that is horizontal to the floor (Franklin Horizontal Plane). Ask the subject to inhale deeply and maintain a fully erect position without lowering his/her head. Place the plastic board on the highest part of the head, with the board parallel to the ground. Compress any hair. Read height to the nearest 1/2". Only a single measurement needs to be made.

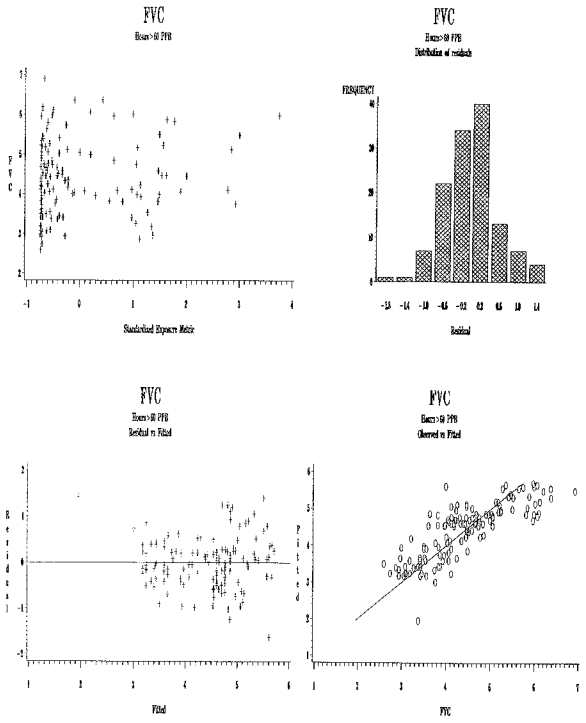
2. Laboratory Visit: Procedure

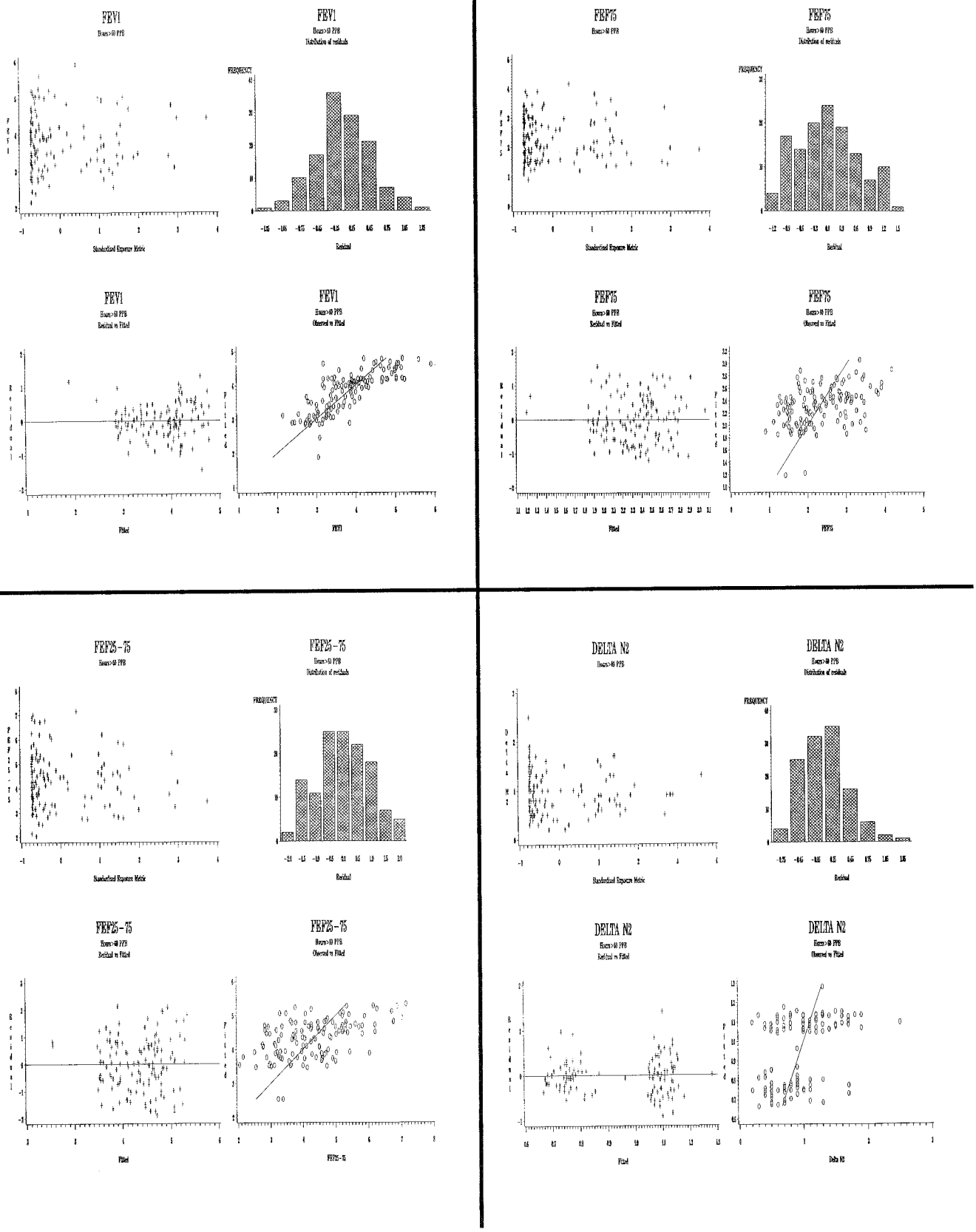
a. The procedure is essentially the same as that performed in the home, except that a wall-mounted stadiometer will be used in the laboratory.

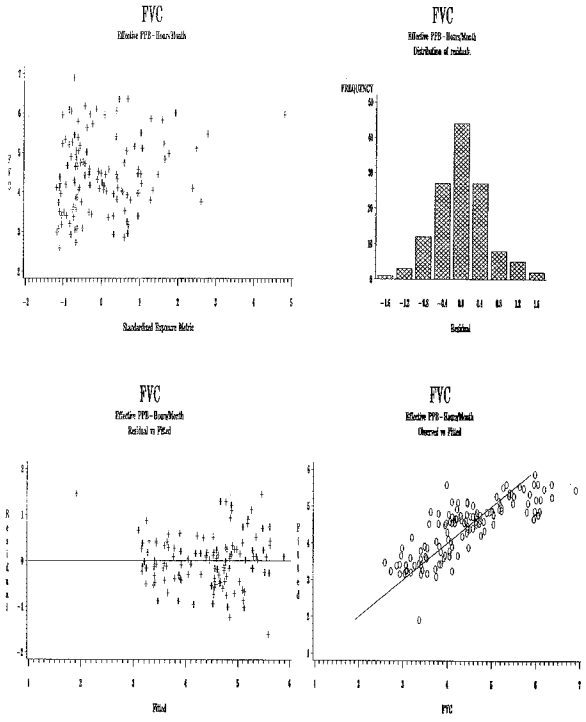
APPENDIX D. Plots of Regression Diagnostics for Regressions of Measures of Pulmonary Function on Standardized Estimated Lifetime Ozone Exposures

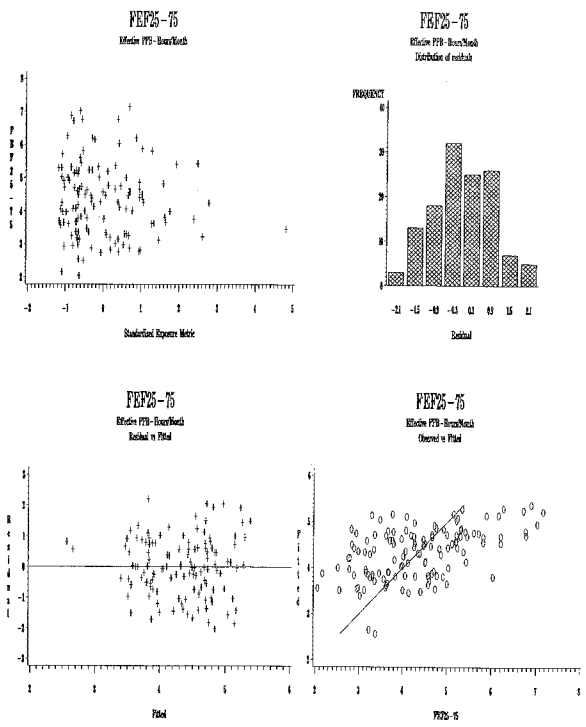
Selected regression diagnostics are provided for the application of the main model to hours above 60 ppb and effective ppb-hours per month based on the 10 a.m. to 6 p.m. average ozone concentrations. For each measure of lung function, four plots are provided on each page:

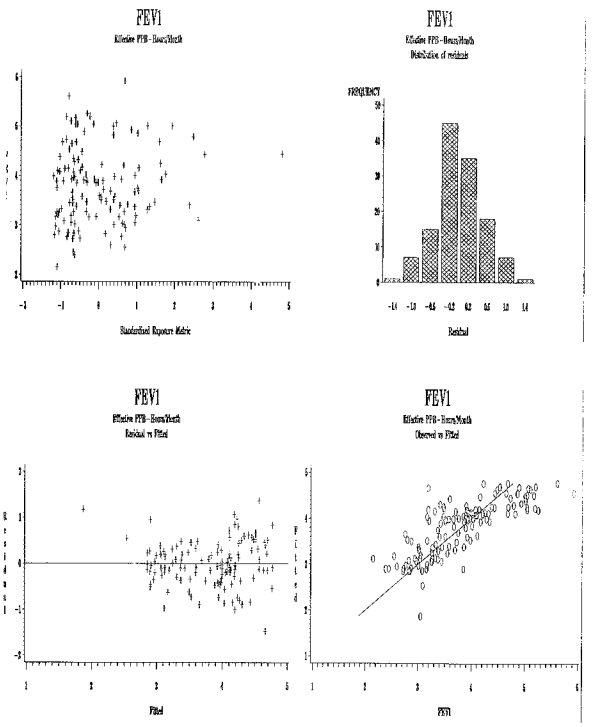
Upper left	Observed values for measure of lung function versus standardized exposure metric (see Analyses of the Relation Between Effective Lifetime Exposure to Ozone and Pulmonary Function section for definition);
Upper right	Histogram of residuals for measure of function;
Lower left	Residuals of measure of function versus fitted values (from regression) of the measure of function; and
Lower right	Fitted values of the measure of function versus the observed values (solid line indicates line of identity for fitted and observed values).

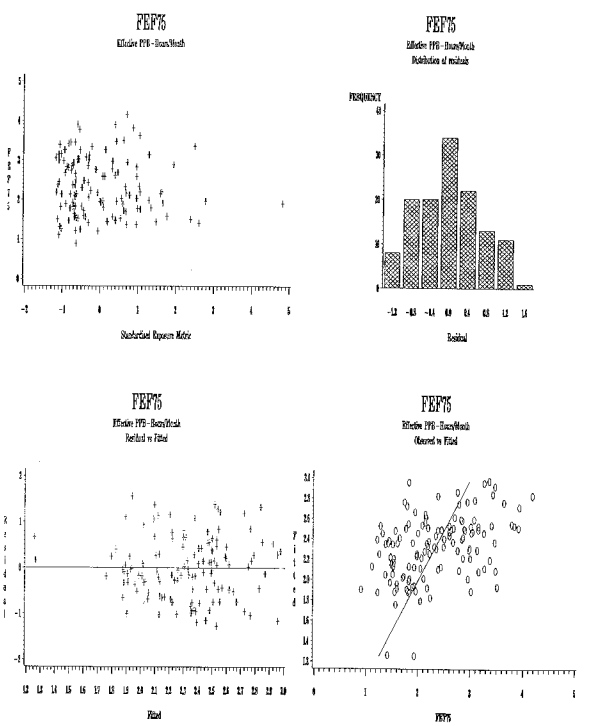


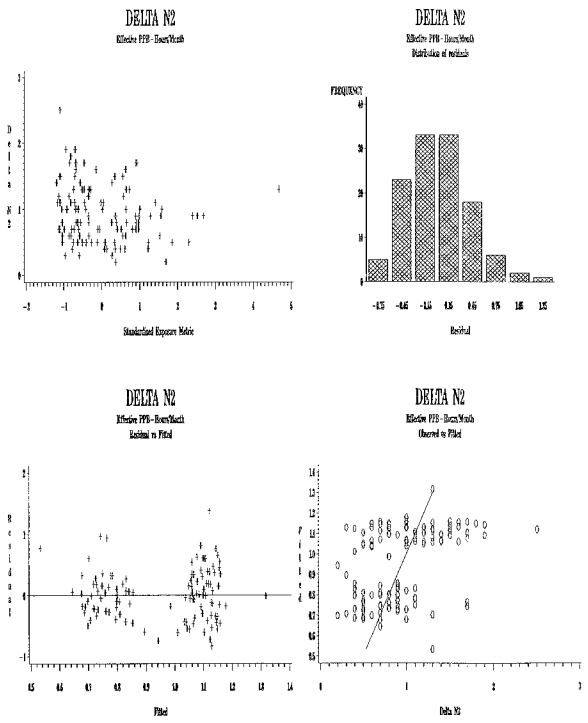

FEV1
Hosm>40 PPB
FEV1
Hosm>40 PPB
Distribution of residuals
FREQUENCY
Standardized Exposure Metric
Residual
FEF75
Hosm>40 PPB
FEF75
Hosm>40 PPB
Distribution of residuals
FREQUENCY
Standardized Exposure Metric
Residual
FEV1
Hosm>40 PPB
Residual vs Fitted
Residual
Fitted
FEV1
Hosm>40 PPB
Observed vs Fitted
Fitted
FEV1
FEF75
Hosm>40 PPB
Residual vs Fitted
Residual
Fitted
FEF75
Hosm>40 PPB
Observed vs Fitted
Fitted
FEF75
FEF25-75
Hosm>40 PPB
FEF25-75
Hosm>40 PPB
Distribution of residuals
FREQUENCY
Standardized Exposure Metric
Residual
FEF25-75
Hosm>40 PPB
Residual vs Fitted
Residual
Fitted
FEF25-75
Hosm>40 PPB
Observed vs Fitted
Fitted
FEF25-75
DELTA N2
Hosm>40 PPB
DELTA N2
Hosm>40 PPB
Distribution of residuals
FREQUENCY
Standardized Exposure Metric
Residual
DELTA N2
Hosm>40 PPB
Residual vs Fitted
Residual
Fitted
DELTA N2
Hosm>40 PPB
Observed vs Fitted
Fitted
Delta N2


FVC
FVC
FVC
FVC


FEF25-75
FEF25-75
FEF25-75
FEF25-75


FEV1
FEV1
FEV1
FEV1


FEF75
FEF75
FEF75
FEF75



ABOUT THE AUTHORS

Ira B. Tager is a Professor in the Division of Public Health Biology and Epidemiology, School of Public Health at University of California, Berkeley. He received his M.D. in 1969 from the University of Rochester School of Medicine and his M.P.H. from the Harvard School of Public Health in 1973. Dr. Tager has conducted research on the natural history of chronic obstructive lung disease, the effects of environmental tobacco smoke on the development of chronic respiratory disease, and the respiratory health effects of prolonged exposure to ambient air pollutants.

Nino Künzli holds positions in the Environmental Health Department at the ISPM University in Basel, Switzerland, and in Environmental Epidemiology at the Swiss Federal Institute of Technology, Zurich. He received his M.D. at the University of Basel and an M.P.H. and a Ph.D. (1996, epidemiology) at the University of California, Berkeley. Dr. Künzli's research focuses on the long-term effects of air pollution and on epidemiologic methods for exposure assessment. Dr. Künzli serves as the Swiss Principal Investigator for the European Project on Air Pollution Exposure Distribution Assessment in Urban European Adult Populations.

Frederick Lurmann is a Senior Scientist and Manager of air quality modeling at Sonoma Technology in Santa Rosa, CA. He received his M.S. in mechanical and environmental engineering from the University of California, Santa Barbara. His major research interests are human exposure to air pollutants and air pollution modeling.

Long Ngo received his M.A. in statistics at the University of California, Berkeley, in 1989 and currently is a candidate for a Ph.D. in biostatistics at the same university. Mr. Ngo has provided statistical support for a number of studies related to the epidemiology of chronic lung disease, health effects of air pollution, and personal monitoring for ozone exposure. His statistical research focuses on computational issues in model selection for linear mixed effects and generalized linear mixed effects models.

Mark Segal currently is Associate Professor in the Division of Epidemiology and Biostatistics at the University of California, San Francisco. Dr. Segal received his Ph.D. in statistics from Stanford University in 1986. He has provided original statistical research (nonparametric regression, tree-structured regression) for problems that relate to longitudinal epidemiologic studies of chronic respiratory disease and currently is working on several projects that relate to acute and chronic health effects of air pollution.

John Balmes received his M.D. from The Mount Sinai School of Medicine of the City University of New York. Since 1986 he has been on the faculty of the Department of Medicine at the University of California, San Francisco, where he is currently Associate Professor, Director of the Human Exposure Laboratory in the Lung Biology Center, and Chief of the Division of Occupational and Environmental Medicine at San Francisco General Hospital. His research interests are the respiratory health effects of air pollution and occupational lung diseases.

PUBLICATIONS RESULTING FROM THIS RESEARCH

Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. 1996. Reliability of life-time residential history and activity measures as elements of cumulative ambient ozone exposure assessment. J Expos Anal Environ Epidemiol 6(3):289–310.

Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. 1997. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen: Results of a pilot study. Environ Res 72(8):8–23.

Künzli N, Kelly T, Balmes J, Tager IB. 1997. Reproducibility of retrospective long-term assessment of outdoor time-activity patterns as individual determinants of long-term ambient ozone exposure. Int J Epidemiol 26(6):1258–1271.

Künzli N, Tager IB. 1997. The semi-individual study in air pollution epidemiology: A valid design as compared to ecologic studies. Environ Health Perspect 105(10):1078–1083.

ABBREVIATIONS

A	proportion of concordant pairs
ANOVA	analysis of variance
CARB	California Air Resources Board
CI	confidence interval
DN_2	slope of phase III of the single-breath nitrogen washout curve
ELT	effective lifetime (exposure)
EPA	U.S. Environmental Protection Agency
$FEF_{25\%-75\%}$	forced midexpiratory (maximum) flow (between 25% and 75% of the FVC)
$FEF_{50\%}$	forced expiratory (instantaneous) flow at 50% of FVC
$FEF_{75\%}$	forced expiratory (instantaneous) flow at 75% of FVC (point at which 75% of FVC has been exhaled)
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
I/O	indoor/outdoor ozone concentration ratio
LAB	Los Angeles Basin
MEFV	maximum expiratory flow-volume (curve)
MET	metabolic equivalent
NO_2	nitrogen dioxide
P_a	expected prevalence of a "Yes" response
PM_{10}	particulate matter less than 10 μm
ppb	parts per billion
SBNW	single-breath nitrogen washout (test or curve)
SD_{diff}	standard deviation of the difference between estimates from test sessions 1 and 2
SD_{av}	standard deviation of the average of estimates from test sessions 1 and 2
SFBA	San Francisco Bay Area
T	effective exposure time

INVESTIGATORS' REPORT

Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure

Part III: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (U.S. Sites)

Patrick L. Kinney, Maneesha Aggarwal, Sergey V. Nikiforov, and Arthur Nadas

ABSTRACT

Methods are needed for retrospective estimation of long-term ozone exposures in epidemiologic studies. The overall objective of this study was to evaluate whether data from available U.S. ozone monitoring sites are useful for estimating lifetime ozone exposures of young adults (for example, college students). Several aspects of this question were evaluated. First, we applied and compared several spatial interpolation methods to a set of long-term average ozone data from all U.S. monitoring sites in operation from 1981 through 1990. Interpolation methods included simple and weighted averages, linear regression, and, in an exploratory way, kriging. The comparison of methods was carried out for five different metrics of ozone concentration: the daily one-hour maximum (MAX1)* and eight-hour maximum (MAX8), the average ozone concentrations between 10 a.m. and 6 p.m. (MID8) and between 10 a.m. and 10 p.m. (MID12), and the sum of all hourly ozone concentrations greater than or equal to 60 parts per billion (ppb) (SUM06).

We also tested whether interpolations were improved by modeling the influence of covariates such as population density, elevation, and weather on ozone concentrations. We analyzed the reliability of a set of newly developed questions about past activity levels among a group of 52 freshmen students at Yale University. This was done by analyzing the agreement between answers to the same questionnaire administered two times, one month apart (test and retest), to the same students. Finally, we combined the interpolation models with residential history information obtained by questionnaire to derive long-term ozone exposure estimates for a group of 200 Yale freshmen.

Results of our study showed that the density of available monitoring sites appears to be adequate for estimating spatial patterns of long-term average ambient ozone concentrations. A simple regression-based interpolation on the three nearest sites produced consistently good results. Including covariates in the interpolation models did not substantially improve the estimates. The largest estimation errors ocurred for areas where ozone concentrations were highest. The newly developed activity history questions exhibited fair to moderate reliability. The results of this work imply that reasonably precise estimates of long-term ambient ozone concentrations for use in large-scale epidemiologic studies can be achieved by interpolating ozone concentrations between available U.S. monitoring sites. This study did not address the issues of whether and how retrospective data on factors that modify exposure or dose (e.g., indoor/outdoor penetration of ozone and time outdoors) can be used to derive estimates of long-term personal ozone exposures and contribute to the assessment of received dose.

INTRODUCTION

The acute effects of ozone on human pulmonary function are well documented in both controlled exposure and epidemiologic studies (Horstman et al. 1990; Spektor et al. 1991); however, the public health significance of these short-term, generally reversible effects remains uncertain. Of greater public health concern would be persistent changes in pulmonary structure or function that develop over many years of ozone exposure, like those documented in long-term animal studies (Tyler et al. 1988). Whether such changes occur in humans is one of the major remaining uncertainties regarding ozone health effects (Tager 1993).

To address the chronic effects of ozone epidemiologically requires reliable methods for estimating long-term exposures of the individuals under study. The exposure assessment problem has two components: first, interpolat-

* A list of abbreviations appears at the end of the Investigators' Report.

This Investigators' Report is Part III of Health Effects Institute Research Report Number 81, which also includes *Part I: Variability of Pulmonary Function Measures*, by Dr. Ira Tager and associates; *Part II: An Approach to Retrospective Estimation of Lifetime Ozone Exposure Using a Questionnaire and Ambient Monitoring Data (California Sites)*, by Dr. Ira Tager and associates; a Commentary by the Health Review Committee on all three Investigators' Reports; and an HEI Statement about the research projects. Correspondence concerning the Part III Investigators' Report may be addressed to Dr. Patrick Kinney, Columbia University School of Public Health, Division of Environmental Sciences, 60 Haven Avenue, B-1, New York, NY 10032.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

ing ambient ozone measurements from the points of measurement to the locations where people live, and second, estimating individual exposures and doses conditional on ambient concentrations in the residential area. The present project focused primarily on methods to address the first component of the problem.

Among the few epidemiologic studies that have addressed the respiratory effects of long-term ozone exposures, exposure assessment methods have ranged among simple assignment to high-exposure and low-exposure categories (Detels et al. 1987), computing annual average ozone concentrations from sites within the study areas (Schwartz 1989), and simple interpolations from nearby sites weighted by inverse distance in specific areas (Abbey et al. 1991a,b). Few studies have assessed exposures over periods long enough to constitute a significant fraction of the subjects' lifetime exposure history. In addition, the geographic range of study populations has been limited. Most studies have been carried out in California, where the longest and most extensive record of ozone monitoring exists.

Since 1981, an extensive, high-quality, ozone monitoring network that spans the entire United States has been in place. The data from that network are now available in digital form on a data base maintained by the U.S. Environmental Protection Agency (EPA). Routine use of this rich data resource in epidemiologic studies of long-term ozone effects has been hindered by feasibility constraints and by uncertainties about the spatial representativeness of the monitoring network.

Students attending college are an attractive population in which to study the human health effects of long-term exposure to air pollution for several reasons. This population is old enough to have experienced long-term exposure to air pollution, but too young to have experienced extensive occupational exposures that could confound the analysis. Residential histories of this population are relatively simple (i.e., most 18-year-olds have lived in fewer than three locations) and easy to document retrospectively. Nationwide air monitoring data that span their entire lifetime can in principle be matched with residential histories obtained by questionnaire to construct profiles of long-term air pollution exposure. The 18 years leading up to college constitutes a period of life during which people are typically physically active and more likely to spend time outdoors, two factors that increase the received dose of air pollution at a given exposure concentration. In colleges that attract students from across the country, a broad and representative range of long-term pollution exposure histories should be available for study. Finally, the college setting simplifies the logistics of collecting health data (e.g., pulmonary function measures). For these reasons, the college years present a window of opportunity for the epidemiologic study of long-term air pollution effects.

SPECIFIC AIMS

The present study focused on improving the tools available to epidemiologists for assessing long-term human exposure to air pollution in nationwide studies of young adults. The specific aims of this study were to:

1. Evaluate the adequacy of existing ozone data from U.S. monitoring stations for retrospective exposure assessment in college-age cohorts.
2. Develop, test, and evaluate a set of questions for collecting key data relating lifetime personal activity patterns and ozone exposures in the communities in which college freshmen had lived.
3. Estimate lifetime ozone exposures for a sample of 200 college freshmen, and evaluate the range and uncertainty of these estimates over space and time.
4. Design a cohort study addressing functional effects of long-term ozone exposures in college students.

METHODS

DATA RETRIEVAL AND PROCESSING

Hourly ozone measurements were obtained from all U.S. monitoring sites in operation from 1981 through 1990 (inclusive) for which data were available on the Aerometric Information and Retrieval System (AIRS), a computerized data base maintained by the EPA. The AIRS data base serves as the central repository of all routine air monitoring data collected in the United States. The number of ozone monitoring sites increased rapidly in the late 1970s, reaching a plateau of more than 600 sites in 1981. Hourly ozone data on AIRS were downloaded in the AMP355 format to site-specific files, each uniquely identified by a standard nine-digit code (two digits for the state, three digits for the county, and four digits for the site). From the AMP355 file, we extracted the site identification, date, hour, and ozone concentration. The hourly ozone observations were then converted to daily and monthly ozone summary metrics (see below). This processing was carried out using FORTRAN and SAS programs (SAS Institute, Cary, NC), yielding as output two SAS data sets, one containing daily ozone records, and the other containing monthly ozone records.

Because it is not clear what measure of daily ozone concentration is most relevant to human health effects, we

computed five separate ozone metrics. The MAX1 metric is the daily one-hour maximum ozone concentration, the measure by which the ambient air quality standard was previously defined. MAX8, the daily maximum eight-hour running average, is the measure used for the current ozone standard. MID8 and MID12 are unique in that they average over the specific hours of the day when people tend to be most active—that is, between 10 a.m. and 6 p.m. and between 10 a.m. and 10 p.m., respectively. The SUM06 metric, which is the sum of hourly concentrations of 60 ppb or higher, incorporates the concept of a threshold (60 ppb) below which hourly concentrations are assumed to be irrelevant. SUM06 has been used extensively in crop-loss studies and was included here for completeness.

As a way of addressing gaps in the available raw hourly data, we arbitrarily chose to compute a summary metric if at least half of the possible hours were available for the computation. Thus, if fewer than 12 hourly ozone observations were available in a day, MAX1 and SUM06 were set to "missing." If between 12 and 23 valid hourly ozone values were available for a given day, the SUM06 value for that day was adjusted upward in proportion to the ratio of 24 hours to the number of hours with data. If fewer than five 8-hour running averages were available in a day, MAX8 was set to missing; if fewer than four hourly values were available between 10 a.m. and 6 p.m., MID8 was set to missing; if fewer than six hourly ozone values were available between 10 a.m. and 10 p.m., MID12 was set to missing.

Monthly means were computed of each daily ozone metric (except SUM06, for which the monthly sum was computed). In all cases, valid daily values for at least half of the days in a month were required in order to compute the monthly metric. When some days were classified as missing, monthly SUM06 was adjusted upward in proportion to the ratio of total days in the month to valid days in the month.

For interpolation modeling in the present project, the monthly data were averaged to obtain the 10-year average of ozone concentrations over the summer season (that is, June, July, and August) for each of the five metrics. These 10-year summer means were used in most of the analyses described below.

INTERPOLATION OF OZONE CONCENTRATIONS

A major goal of this project was to determine the quality of long-term ozone exposure estimates that can be obtained by interpolation from available U.S. ozone monitoring sites. Such interpolations, if reliable, would have value in estimating individual ozone exposures in epidemiologic studies addressing the respiratory health effects of long-term ozone exposure.

We tested several different methods of interpolation, and compared the magnitudes of the interpolation errors across methods. Interpolation quality was quantified using the root mean square of the differences between interpolated summer mean ozone concentrations at the ozone monitoring stations and the actual concentrations measured there. This approach provides a direct measure of interpolation quality—that is, the SD of the residuals (observed minus predicted values)—and a measure by which alternative interpolation methods could be compared.

Four interpolation methods were tested on the full data set. The computations involved in each method can be described mathematically as follows:

(1) simple average of k nearest sites,

$$\hat{O}_0 = \frac{1}{k}\sum_{i=1}^{k} O_i;$$

(2) inverse-distance–weighted average of k nearest sites,

$$\hat{O}_0 = \left(1/\sum_{i=1}^{k}\frac{1}{d_i}\right)\sum_{i=1}^{k} O_i \bullet \frac{1}{d_i};$$

(3) inverse-distance-squared–weighted average of k nearest sites,

$$\hat{O}_0 = \left(1/\sum_{i=1}^{k}\frac{1}{d^2_i}\right)\sum_{i=1}^{k} O_i \bullet \frac{1}{d^2_i};$$

(4) regression on k nearest sites,

$$\hat{O}_0 = \alpha + \sum_{i=1}^{k} \beta_i O_i;$$

where $\hat{O}_0$ = estimated summer mean concentration at site 0; O_i = summer mean ozone concentration at the ith nearest site; d_i = distance to ith nearest site; α = intercept term; and β = slope relating ozone at site 0 to ozone at nearest sites 1 to k.

These methods can all be thought of as members of a larger class of linear models that involve linear combinations of ozone data from surrounding sites. For example, methods 1, 2, and 3 are special cases (with exponents 0, 1, and 2) of a more general class of methods in which the exponent of distance is treated as a free parameter. Further, method 4 can be thought of as a generalization of methods 1, 2, and 3 in which the data themselves dictate the weighting coefficients. Understanding these relations among methods leads to the a priori expectation that method 4 will best fit the data.

Method 4 (regression) utilizes data from surrounding sites only on the basis of their ranked nearness to the site being estimated. Intersite distances are not explicitly utilized in this method. Methods 2 and 3 do use distance, but

only to derive relative weights. None of the four methods uses distance in a direct way in the interpolations. We chose this "nearness-based" approach on the basis of preliminary analyses suggesting that spatial variations in ozone concentrations were a stronger function of nearness than of distance. For example, we observed that the absolute differences in ozone concentrations between pairs of nearest sites were nearly constant, averaging between 4 and 6 ppb for all intersite distances up to 100 miles (Figure 1).

Interpolation methods 1 through 4 were each applied in turn to estimate summer mean ozone concentrations at all U.S. monitoring sites using data from k nearest sites. This was done for values of k ranging from 1 to 10, and was repeated for each of the five ozone metrics (that is, MAX1, MAX8, MID8, MID12, and SUM06). In each case, the SD of the residuals (observed minus predicted values) was computed. The interpolation algorithms were implemented using the statistical programming language S-Plus (MathSoft, Seattle, WA).

Interpolation outliers—that is, those monitoring sites for which interpolation residuals were large—were examined to determine whether geographic patterns were evident. This work was carried out for the residuals of the regression method with $k = 3$ applied to the MAX1 ozone metric. The 20 largest outliers were selected for geographic display.

Expanded Regression Method

After the initial interpolation modeling, which based ozone estimates solely on ozone data from nearby sites, we next explored whether augmenting the interpolation with several potentially important covariates would improve the quality of estimation. The covariates included three meteorologic variables (mean summer temperature, relative humidity, and wind speed from the three weather stations nearest the ozone monitoring site), population density in the census tract occupied by the site and in the two nearest census tracts, and site elevation. The meteorologic data were obtained from the International Station Meteorological Climate Summary of the National Climatic Data Center (Asheville, NC). We retrieved multiyear averages of monthly weather data for 308 U.S. weather stations in operation between the 1950s and the early 1990s. Temporal coverage varied somewhat by site. Data for June, July, and August were averaged, yielding mean summer data for each site for the three meteorologic parameters (temperature, relative humidity, and wind speed). The three weather stations closest to each ozone monitoring site were identified using longitude and latitude coordinates. Population density data for all U.S. census tracts were from 1990 census data (obtained from Wessex, Inc., Burlington, MA). The centroid longitude and latitude coordinates of census tracts were used to identify the three tracts nearest to each ozone monitoring site (note that the nearest tract was that in which the ozone monitoring site was located). Population density was viewed as a surrogate for emission density of ozone precursors. The elevation of each ozone monitoring site was obtained from the AIRS data base.

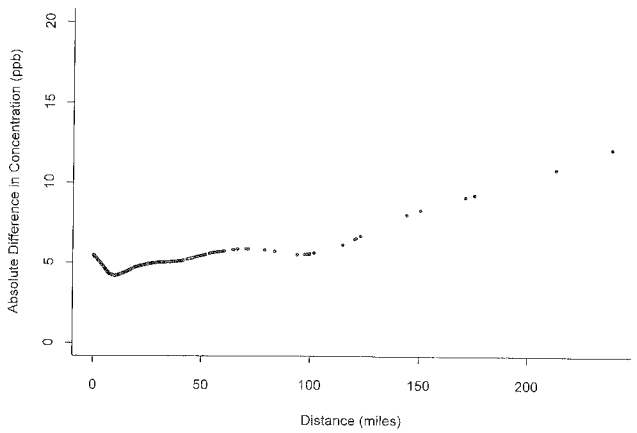


Figure 1. Locally weighted smoothing scatterplot (LOESS) of absolute differences in ozone concentrations between pairs of nearest sites, as a function of the distance between the sites.

Covariate modeling was carried out in the context of a regression model (method 4 above) that included the three nearest ozone monitoring sites (that is, $k = 3$) along with the meteorologic, population density, and elevation covariates discussed above. The SD of interpolation residuals and multiple correlation coefficient squared (R^2), which is, the proportion of variance explained by the model, were used as measures of model quality.

Distance-Based Methods

As noted, the four interpolation methods evaluated above do not take explicit account of intersite distances. To explore whether explicit consideration of distance would improve interpolation results, we carried out two secondary analyses. First, we used the basic three-site regression interpolation method again for three subsets of sites: those for which the nearest site was within 10 miles; those for which the nearest site was between 10 and 30 miles away; and those for which the nearest site was more than 30 miles away. Because of the relation between monitoring site density and population density, this also provides an approximate classification of sites onto a gradient leading from urban to rural areas.

Second, we tested a distance-based method, kriging (Cressie 1989), on data subsets. Universal kriging amounts to fitting a process of the form

$$Z(x) = f(x)^T\beta + \epsilon(x),\ f(x) = \{f_1(x),\ldots,f_p(x)\}$$

by generalized least squares, predicting the value at location x of both terms, and taking their sum. The term $f(x)^T\beta$ represents the trend, and $\in(x)$ the random fluctuation. Subscript p is the order of trend surface, and β is the coefficient of least squares for f_1 to f_p (Ripley 1981).

Kriging begins with estimation of the "variogram," a function relating the variance of pairwise intersite differences in concentration to the distance between the sites. The variogram, which is closely related to the autocovariance function, is then used to estimate parameters of a linear prediction model that weights concentrations measured at nearby sites on the basis of their distance from the site to be estimated.

For the kriging analysis, we used the "surf.1s" program of the spatial functions obtained from the S-Plus software library. This uses covariance function C such that $C(x,y) = c[d(x,y)]$, where c is the correlation and d is the Euclidean distance. This implicity rescales x and y to [–1,1], which ensures that the first few polynomials are far from collinear. A correlogram was computed by dividing the distance into 67 bins and finding the covariance between pairs whose distance falls into each bin, then dividing by the overall variance.

The variogram was then used to estimate parameters of a linear prediction model based on their distance from the site to be estimated. The variogram computed from the kriging results is related to C by

$$V(x,y) = 1/2\ [C(x,x) + C(y,y)] - C(x,y) = c(0) - c[d(x,y)]$$

Kriging was applied to two subsets of the 10-year summer mean data set: the entire state of California (122 sites), and the three-state region of New York, New Jersey, and Connecticut (NY/NJ/CT) (69 sites). Correlograms and variograms were created and polynomial curves of order 2 were fitted to the variogram. Residuals were computed from the data, and the residual mean square error was compared with the regression method for the same data set, based on the 10 nearest sites.

Kriging usually fits very precise estimates of ozone concentrations at monitoring locations. More relevant to the exposure estimation problem is the quality of estimates for unmeasured locations. To address this problem, we split the data in each region into two portions. Two thirds of the sites (chosen at random) were used for parameter estimation, with the remaining one third used for estimation and error analysis. For comparison, we also tested the regression method in the same way.

ACTIVITY HISTORY QUESTIONS

In order to use ambient ozone data to estimate long-term exposures of individuals in the context of epidemiologic studies, individual-level data are needed on residential histories and other factors assessed over long time periods. Outdoor activity patterns are important determinants of individual ozone doses conditional on ambient concentration. At a constant ambient concentration, subjects who spend more time outdoors and more time engaged in vigorous activities outdoors will tend to have larger ozone than do other subjects. One goal of our work on this project was to develop and test a set of questions that retrospectively assessed these and other factors over the entire lifetime of a young-adult population.

Activity questions were developed as described below and included in a larger questionnaire that was self-administered by a group of freshmen at Yale University (Appendix A). The questionnaire assessed several factors besides lifetime activity patterns, including such indoor factors as use of gas stoves and air conditioners. However, the analyses presented here focused on evaluating the test-retest reliability of a set of five questions (questions 39 through 43) developed to retrospectively assess lifetime activity patterns and levels (see Table 11 in the Results section). These questions were singled out for reliability analysis because, in contrast to most of the other questions, they were newly developed for this study.

Our activity questions were based on a set of questions developed and tested by Dr. Ira B. Tager and his colleagues in the study reported as Part II of this Research Report (see Appendix A, Part II). However, the activity questions in the present study were referenced to specific life epochs rather than to specific residences. Activity patterns during four life epochs were assessed in our questions: before age 6, during elementary school, during middle school, and during high school. The questions addressed both summer and school-year activities. Assessing activity within consistent life epochs, rather than with reference to specific residences (the number and timing of which vary across individuals), provides time references that are consistent among individuals. This new approach may facilitate application of activity data as modifiers of exposure or received dose within specific periods of life that differ in terms of exposure or lung development or both.

The reliability of questions 39 through 43 was analyzed by administering the questionnaire twice, approximately one month apart, to a set of 52 Yale freshmen as part of an ongoing National Institutes of Health–funded epidemiologic study assessing respiratory health in young adults. The initial measurements were collected during pilot sampling at Yale in late February 1995. A total of 116 subjects completed the questionnaire during the pilot study. The follow-up measurements were carried out in late March and early April when the first full cohort of subjects ($N = 624$)

was recruited for the larger study. Fifty-two subjects completed questionnaires for both the pilot and main studies. All subjects read and signed an informed consent form approved by the Columbia Health Sciences Institutional Review Board and the Yale Human Investigations Committee.

Analyzing the consistency in questionnaire responses across two separate occasions provides a measure of the questionnaire's "reliability," but not of the veracity or "validity" of the responses. Good reliability is consistent with, but does not prove, validity. Reliability of the activity questions was analyzed by computing simple and weighted kappa statistics (Fleiss 1981) using the SAS Freq procedure with the Agree option (SAS Institute). The kappa statistic measures the level of agreement between repeated measurements of a categorical variable beyond the agreement that would be expected by chance alone. The weighted kappa accounts for approximate agreement by giving greatest weight to exact agreement (that is, the diagonal of the contingency table) and progressively less weight to off-diagonal elements.

LONG-TERM EXPOSURE ESTIMATION

We utilized the three-site regression interpolation method along with residential history information obtained by questionnaire (with residences resolved to the level of month and town) to retrospectively estimate and analyze long-term ambient ozone exposures for a group of 200 first-year students at Yale University. Of 458 subjects who completed questionnaires in 1996, these, 104 (23%) reported living outside the United States for more than one year and were excluded from the exposure analysis. From the remaining 354 subjects, we randomly selected 200 for whom we estimated long-term ozone exposure. The group was equally split among men and women, and ranged in age from 17.5 to 21 years (mean = 18.9 years). The racial distribution was as follows: white (66%), black (7.5%), Hispanic (5.5%), Asian (15%), and other (6%).

Estimates of the summer mean for daily eight-hour maximum ambient ozone concentrations in residential locations were obtained by interpolation from the three nearest monitoring sites. Town centroids were geocoded according to latitude and longitude coordinates. Interpolations were carried out by the regression method described above, which exhibited relatively low interpolation errors.

Two alternative methods were used to compute individual long-term ozone exposures, one time-independent and the other time-dependent. For the time-independent method, each residential location was characterized by a single, time-invariant ozone estimate obtained by interpolation from monitoring site data averaged over all available years in the period 1981 through 1990. Individual 10-year exposure estimates were then calculated by averaging over all residences for a given subject, weighted by the number of years at each residence.

For the time-dependent method, year-specific exposure estimates were obtained for each subject at each residential location by interpolation from monitoring site data available for each separate year. The result was a 10-year series of annual exposure estimates for each individual that typically covered the period between ages 4 and 13. To compute long-term exposures, we averaged the annual exposure estimates over 10 years for each subject.

Operationally, the time-independent method was simpler to carry out, and utilized all available sites (n = 1,112) for the interpolations, but had the drawback of ignoring year-to-year variations in concentrations. The time-dependent method captured temporal variations in concentrations, but was slightly more laborious because it required annual interpolations.

The distributions of long-term ozone exposure estimates obtained by the two methods were examined and compared. In addition, we carried out a nested random effects analysis of variance using the annual estimates from the time-dependent method, yielding estimates of both the within-person and between-person variations in exposures. These variance estimates can be used to perform sample size calculations in designing future epidemiologic studies.

QUALITY ASSURANCE

The data analyzed in this study were subjected to several levels of validation and review. The primary purpose of this effort was to verify that no errors were introduced as the data passed through the processing stream, from initial raw data records to the final data sets used for analysis. A secondary purpose was to evaluate in general terms the adequacy of routine site operation procedures used in generating the raw data.

Data processing was verified in several ways. A written procedure was developed and used for retrieving and processing hourly ozone records from the EPA AIRS data base. Any error messages generated by the SAS system during routine data processing were printed on the screen and followed up immediately. Listings of program logs and data summaries for each site were printed on paper, reviewed by the principal investigator, and kept on file. Merging of the site-specific monthly summary files into a single national data base and computation of 10-year summer means were carried out directly, or under close supervision, by the principal investigator. Dated records of all data processing tasks and corresponding data sets were kept on file.

As a final check of the data processing system, a randomly selected subset of 177 sites were reretrieved from the AIRS data base and reprocessed by an independent technician. The ozone means were then compared with those processed initially. This level of verification (n = 177) was chosen on the basis of hypergeometric sampling theory in order to have 90% confidence that the error rate was less than 1% in the full data base of 1,112 sites. Complete agreement was observed.

The secondary quality assurance objective, to evaluate in general terms the adequacy of routine site operation procedures used in generating the raw data, was carried out by a telephone survey of routine operating procedures used at a random subset of monitoring sites. Methods used for maintaining and calibrating ozone monitors can affect the accuracy of the measurements reported by those monitors. Of particular importance is the method used to deliver calibration gas to the monitor; this can be done either directly at the monitor inlet or through the sample line and filter leading to the monitor. The latter approach is preferable in that long sample lines and dirty filters can serve as ozone sinks. This problem was noted at several monitoring sites audited by New York University staff (Mr. John Gorczynski, personal communication) in a previous study. Other relevant issues include the frequency of instrument audits by an independent agency, the frequency of instrument filter changes, and the type of ozone instrument used.

A thorough analysis of site operations would require site visits and calibration audits of a representative sample of ozone monitoring sites, an effort beyond the scope of the present study. However, to make a qualitative assessment of these issues, a short questionnaire was developed and administered over the telephone to a random sample of site operators. We randomly selected 79 sites that were in operation in 1990, the most recent year available in our data base, and contacted the agency responsible for monitoring at that site. When possible, the interviewer spoke with the individual who actually operated the site in question. Complete data were obtained for 60 (76%) of 79 sites. The data were summarized in terms of frequencies on key questions relating to ozone sampling and calibration.

RESULTS

DATA SUMMARIES

The ozone data base we constructed spanned the years 1981 through 1990. A total of 1,112 sites had at least one month of valid data during this period (Figure 2 [next page]); however, in any given year, the number of sites in operation ranged from 605 (1981) to 702 (1990) (Table 1). Table 2 presents summary statistics on the entire data set of monthly values. Recall that MAX1 is the daily one-hour maximum, MAX8 is the daily eight-hour maximum, MID8

Table 1. Number of U.S. Ozone Monitoring Sites in Operation Each Year (1981–1990)

Year	Number of Monitoring Sites
1981	605
1982	617
1983	637
1984	617
1985	623
1986	607
1987	640
1988	655
1989	684
1990	702

Table 2. Summary Statistics of 10 Years of Monthly Ozone Metric Data

	MAX1 (ppb) (n = 62,269)	MAX8 (ppb) (n = 61,917)	MID8 (ppb) (n = 62,292)	MID12 (ppb) (n = 62,334)	SUM06 (ppb-hr) (n = 62,269)
Mean	49.0	40.6	39.3	34.4	4,076.1
SD	18.6	15.8	15.8	14.2	5,494.1
Maximum	233	167	166	134	67,791
95th percentile	75	66	64	57	14,835
75th percentile	60	51	50	44	6,092
Median	48	40	39	34	1,924
25th percentile	36	29	28	24	120
Minimum	0	0	0	0	0

is the average concentration between 10 a.m. and 6 p.m., MID12 is the average concentration between 10 a.m. and 10 p.m., and SUM06 is the sum of all hourly concentrations greater than or equal to 60 ppb. As expected, a strong seasonal cycle was evident, as illustrated in the data for MAX1 (Table 3). Also, there were no strong trends over time, as illustrated for MAX1 also in Figure 3.

Table 3. Summary Statistics of 10 Years of Monthly Data for Ozone Metric MAX1

	Jan (n = 3861)	Feb (n = 3888)	Mar (n = 4137)	Apr (n = 5703)	May (n = 6036)	June (n = 6119)	July (n = 6200)	Aug (n = 6262)	Sept (n = 6212)	Oct (n = 5863)	Nov (n = 4143)	Dec (n = 3845)
Mean	29.2	35.9	43.5	51.4	57.3	62.0	64.6	61.9	52.4	41.7	32.6	27.2
SD	8.6	9.3	10.0	10.7	12.4	16.7	18.8	18.4	15.7	12.9	9.8	8.5
Maximum	70	78	107	130	174	215	219	233	198	143	74	68
95th percentile	44	51	60	68	76	86	92	87	76	65	49	41
75th percentile	35	42	49	57	63	70	73	69	58	48	39	33
Median	28	35	43	51	57	61	64	60	50	40	31	26
25th percentile	23	30	37	45	50	53	54	52	44	34	25	21
Minimum	0	1	0	0	0	0	1	2	4	1	0	0

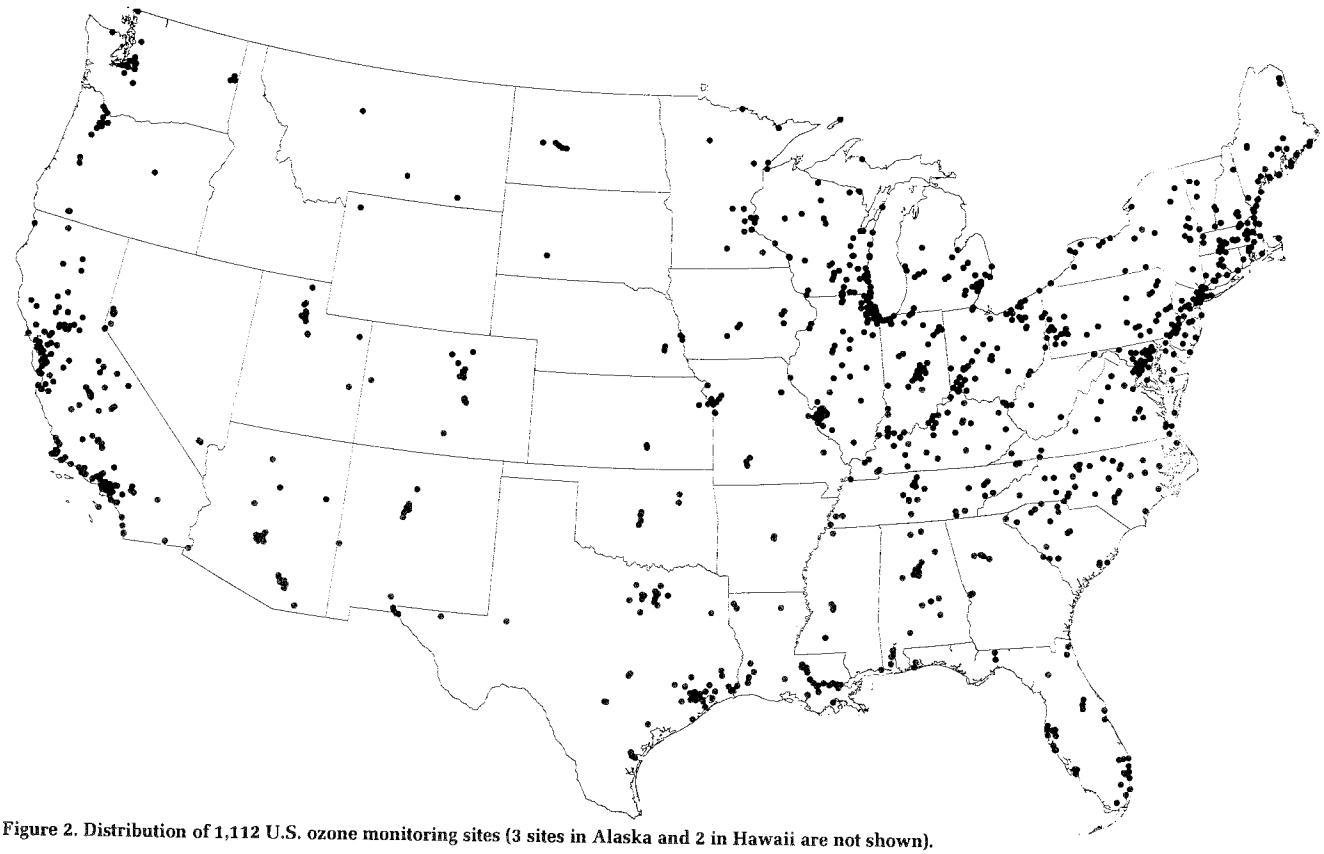


Figure 2. Distribution of 1,112 U.S. ozone monitoring sites (3 sites in Alaska and 2 in Hawaii are not shown).

As noted in the Methods section, interpolation methods were tested using ozone data that were averaged over all years for summer months only. This reduced data set, which had one observation per site on each of the five ozone metrics, is summarized in Table 4. The distributions for all five metrics were unimodal and skewed toward higher concentrations. This is illustrated for MAX1 in Figure 4. The skew was most pronounced for SUM06 (data not shown). Correlations among the five summer mean ozone metrics were high, but correlations involving SUM06 were slightly lower (Table 5).

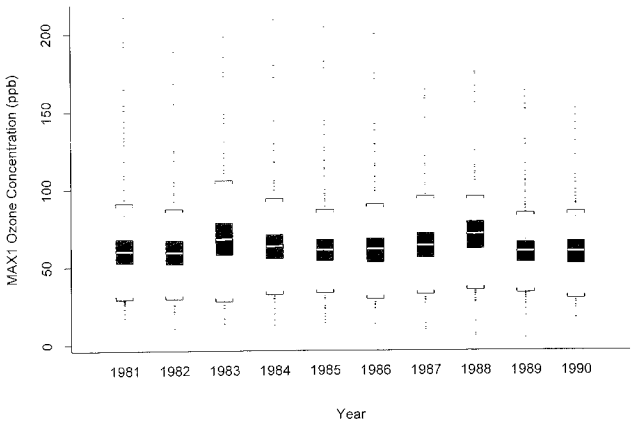


Figure 3. Annual distribution of monthly mean ozone concentration for MAX1. The horizontal line in the interior of each box is located at the median of the data. The height of each box equals interquartile distance, IQD (i.e., 3rd–1st quartile). The dashed lines (whiskers) extending vertically from the top and the bottom of each box extend to the extreme value of the data or 1.5 × IQD (whichever is less). Dashes outside the brackets are the outliers.

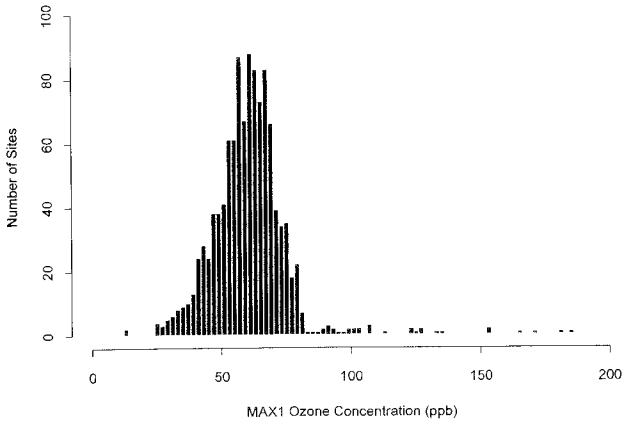


Figure 4. Frequency distribution of summer mean ozone concentrations for MAX1.

Table 4. Summary Statistics of 10-Year Means of Ozone Metric Data for Summer (June–August)[a]

	MAX1 (ppb)	MAX8 (ppb)	MID8 (ppb)	MID12 (ppb)	SUM06 (ppb-hr)
Mean	61.2	51.4	50.0	44.5	7,661.0
SD	15.5	12.3	12.2	10.5	5,697.8
Maximum	185	135	128	117	56,098
95th percentile	79	67	66	59	15,982
75th percentile	68	58	56	50	10,081.5
Median	61	52	50	45	7,076.5
25th percentile	53	45	43	38	4,000
Minimum	13	9	9	7	0

[a] n = 1,112 U.S. monitoring sites analyzed.

Table 5. Correlation Matrix of 10 Years of Summer Mean Ozone Metric Data

	MAX1	MAX8	MID8	MID12	SUM06
MAX1	1.00				
MAX8	0.97	1.00			
MID8	0.97	0.99	1.00		
MID12	0.91	0.98	0.97	1.00	
SUM06	0.89	0.92	0.89	0.91	1.00

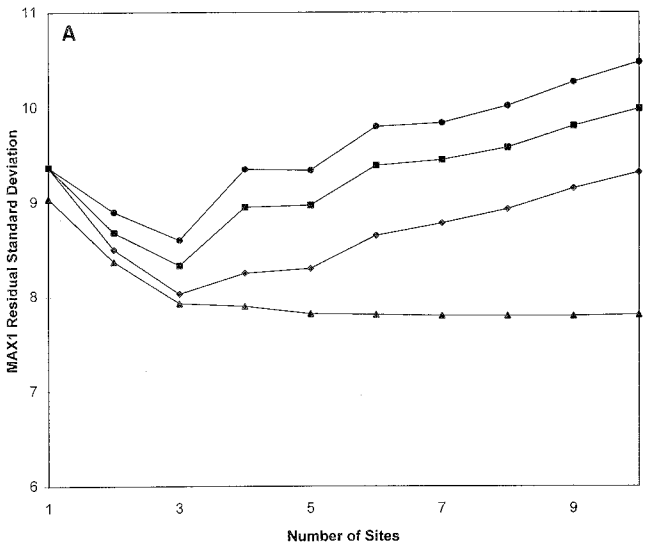
INTERPOLATION OF OZONE CONCENTRATIONS

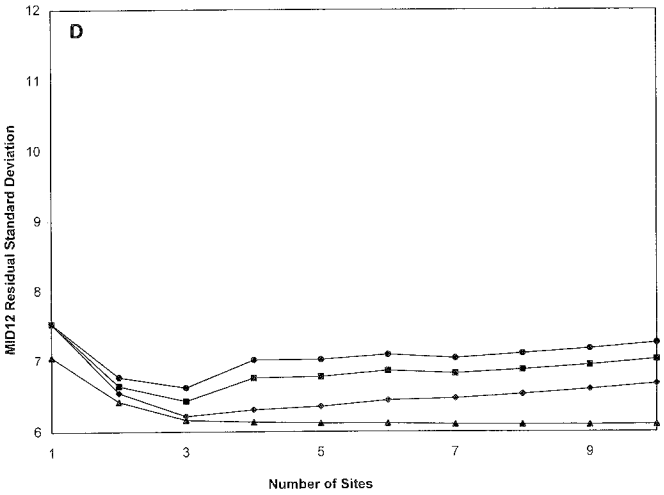
Four interpolation methods were tested on the full U.S. 10-year summer mean data set: simple averaging, inverse-distance–weighted averaging, inverse-distance-square–weighted averaging, and linear regression. For each method, ozone concentrations were predicted using one to ten (inclusive) nearby ozone sites. Ozone concentrations were interpolated to each monitoring site, enabling comparison of the interpolated and actual concentrations at each site. The SD of interpolation residuals (or errors) was used to compare methods. Results are displayed in Table 6 and Figure 5. The regression method slightly outperformed the other methods for all five ozone metrics. For the regression method, error SDs got smaller as the second and third nearby sites were added to the interpolation; however, when more than three sites were added, the marginal improvement diminished. For the other methods, interpolations improved initially but then deteriorated as more nearby sites were included as predictors.

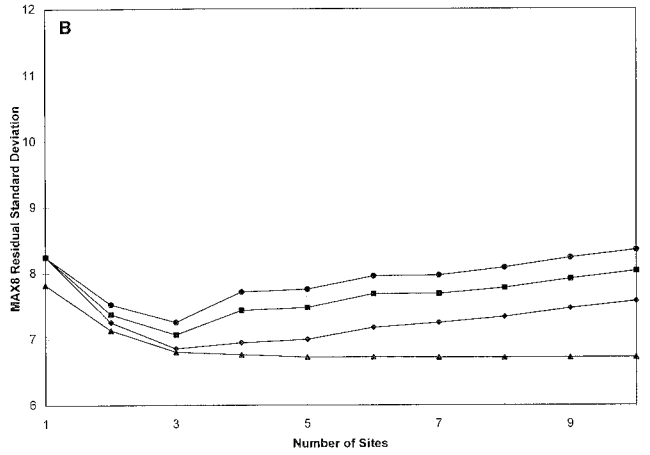
Figure 6 is a scatterplot of observed and predicted data for the regression model applied to the MAX1 metric. Each point represents the observed and predicted concentrations at an individual monitoring site. The error SD for this model was 7.9 ppb, which represented 13% of the mean MAX1

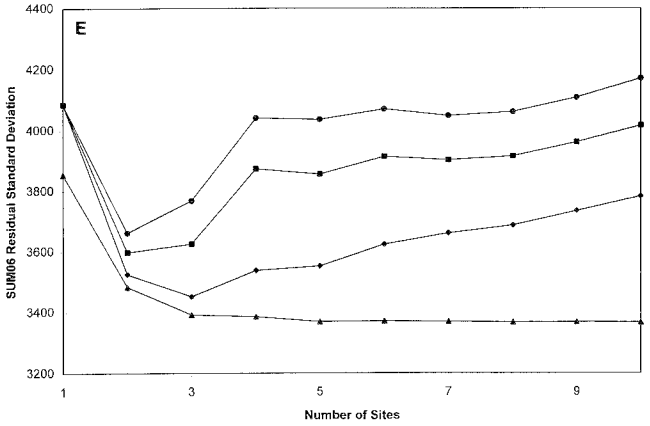
Table 6. Standard Deviations of Residuals (Errors) for Five Ozone Metrics Using Four Interpolation Methods on 1 to 10 Nearest Sites

	Number of Nearest Sites Used for Interpolation									
	1	2	3	4	5	6	7	8	9	10
MAX1										
Simple avg	9.37	8.50	8.03	8.25	8.30	8.65	8.78	8.93	9.15	9.32
Inverse dist	9.37	8.68	8.33	8.95	8.97	9.39	9.45	9.58	9.81	9.99
Inverse dist sq	9.37	8.89	8.60	9.35	9.34	9.80	9.84	10.00	10.30	10.50
Regression	9.04	8.37	7.93	7.90	7.82	7.81	7.80	7.80	7.80	7.81
MAX8										
Simple avg	8.24	7.25	6.85	6.94	6.99	7.17	7.24	7.33	7.46	7.57
Inverse dist	8.24	7.37	7.06	7.43	7.47	7.68	7.68	7.77	7.91	8.03
Inverse dist sq	8.24	7.52	7.25	7.71	7.75	7.95	7.96	8.08	8.23	8.35
Regression	7.82	7.13	6.80	6.76	6.72	6.72	6.71	6.71	6.72	6.72
MID8										
Simple avg	8.22	7.25	6.86	6.92	6.95	7.12	7.18	7.28	7.39	7.49
Inverse dist	8.22	7.38	7.07	7.33	7.39	7.59	7.61	7.69	7.83	7.94
Inverse dist sq	8.22	7.54	7.23	7.59	7.64	7.87	7.88	7.99	8.14	8.26
Regression	7.77	7.12	6.79	6.75	6.71	6.71	6.70	6.99	6.70	6.71
MID12										
Simple avg	7.54	6.55	6.22	6.31	6.36	6.44	6.47	6.53	6.60	6.68
Inverse dist	7.54	6.65	6.43	6.76	6.78	6.86	6.83	6.88	6.95	7.03
Inverse dist sq	7.54	6.77	6.62	7.02	7.02	7.09	7.04	7.11	7.19	7.26
Regression	7.06	6.42	6.16	6.14	6.12	6.12	6.10	6.10	6.10	6.10
SUM06										
Simple avg	4,082	3,524	3,451	3,539	3,552	3,623	3,660	3,685	3,733	3,781
Inverse dist	4,085	3,597	3,624	3,873	3,855	3,913	3,902	3,914	3,960	4,015
Inverse dist sq	4,085	3,661	3,767	4,040	4,035	4,069	4,081	4,060	4,107	4,169
Regression	3,854	3,483	3,391	3,384	3,368	3,370	3,368	3,366	3,366	3,365









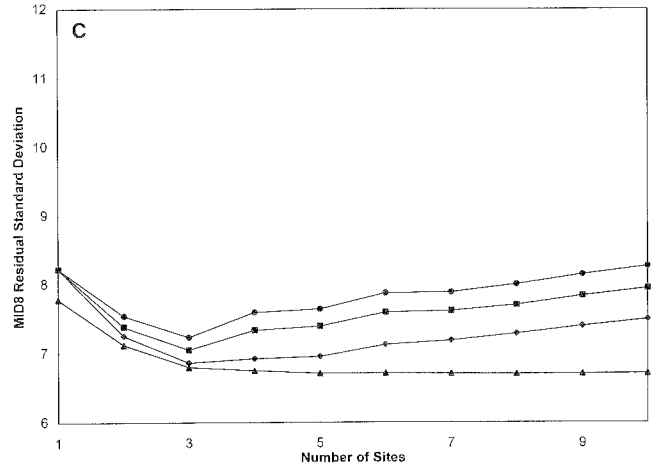


Figure 5. The SD of ozone interpolation residuals (errors) using four methods and 1 to 10 nearest sites for (A) MAX1, (B) MAX8 , (C) MID8, (D) MID12, and (E) SUM06: (◆) simple averaging; (■) inverse-distance–weighted averaging; (●) inverse-distance-squared–weighted averaging; (▲) linear regression.

concentration in this data set. These results demonstrate that reasonably precise estimates of ozone can be obtained for the United States as a whole using a regression-based approach.

Residuals from the regression interpolation for the MAX1 metric were examined. The distribution of interpolation residuals (observed minus predicted values) for the three nearest sites is shown in Figure 7. A map showing the geographic distribution of the 20 largest residuals is presented in Figure 8. Of the 20 largest residuals, 14 (70%)

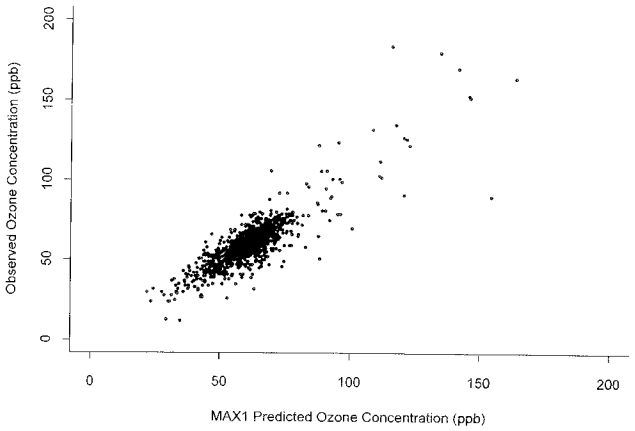


Figure 6. Scatterplot of predicted versus observed summer mean ozone concentrations for MAX1.

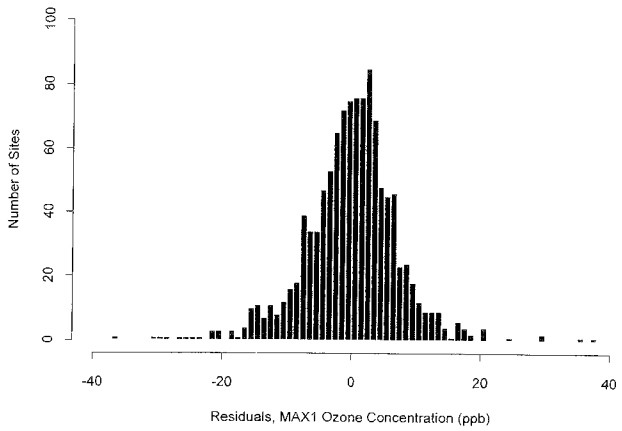


Figure 7. Distribution of residuals from regression on the three nearest sites for MAX1.

Figure 8. Geographic distribution of the ozone monitoring sites where the 20 largest residuals were found using the linear regression prediction method.

were for sites in California, mostly in the vicinity of Los Angeles. Four outlying sites were in the metropolitan NY/NJ/CT area. The remaining outliers were in Massachusetts and Hawaii. A map of the 20 largest relative residuals—that is, where the residual divided by the observed ozone concentration was greatest—revealed a pattern similar to that in Figure 8 (not shown).

To determine whether interpolation errors could be further reduced, the regression on the three nearest sites was augmented with covariates that we hypothesized might improve the interpolations. The covariates included temperature, relative humidity, wind speed, population density, and elevation. Summary statistics on the covariate data are presented in Table 7. Correlations between ozone and the five covariates were modest (Table 8), varying from −0.25 to 0.21. Results of the regression interpolations using the three nearest ozone sites and the five covariates are summarized in Table 9 along with results for the three-site method that did not include covariates. The addition of covariates resulted in very small (essentially negligible) improvements in the explanatory power of the methods beyond that which was obtained by directly interpolating ozone concentrations from the three nearest sites.

To examine the possible role of intersite distance as a determinant of interpolation errors, the basic three-site regression method was used again for three subsets of sites: those for which the nearest site was within 10 miles (n = 632 sites); those for which the nearest site was between 10 and 30 miles away (n = 374 sites); and those for which the nearest site was more than 30 miles away (n = 106 sites). The SDs of the interpolation residuals were 8.6, 7.9, and 7.3 ppb, respectively, for the three data subsets. This suggests

Table 7. Summary Statistics of Covariates[a]

	Temperature (°F)	Relative Humidity (%)	Wind Speed (knots)	Elevation	Population Density
Mean	84.2	49.1	7.6	160.5	1.1
SD	6.7	15.4	2.1	159.3	2.2
Maximum	105	71	12.3	990	40.4
95th percentile	95.3	64	10.3	408	4.2
75th percentile	88.6	56.3	8.7	226	1.5
Median	83.6	53.7	8	140	0.5
25th percentile	80.6	51.3	7	25	0.1
Minimum	52.3	0	0	0	0

[a] n = 1,112 U.S. monitoring sites analyzed.

Table 8. Correlation Matrix of Ozone Metric with Ozone Concentration at the Three Nearest Sites and with Covariates

Ozone Metric	Ozone at Nearest Site	Ozone at 2nd Nearest Site	Ozone at 3rd Nearest Site	Population Density	Elevation	Temperature	Relative Humidity	Wind Speed
MAX1	0.81	0.78	0.75	0.05	0.06	0.17	−0.21	−0.20
MAX8	0.77	0.76	0.72	−0.02	0.12	0.18	−0.21	−0.16
MID8	0.77	0.75	0.71	−0.25	0.12	0.21	−0.21	−0.16
MID12	0.74	0.73	0.68	−0.07	0.18	0.18	−0.20	−0.11
SUM06	0.74	0.73	0.65	0	0.08	0.16	−0.18	−0.15

Table 9. Standard Deviations of the Residuals (Errors) and Multiple Correlation Coefficients Squared of Ozone Modeling Results with Ozone Concentration at the Three Nearest Sites Without and With Five Covariates[a]

	Ozone Without Five Covariates		Ozone With Five Covariates[a]	
Ozone Metric	SD of Residual Error	R^2	SD of Residual Error	R^2
MAX1	7.93	0.74	7.94	0.74
MAX8	6.80	0.69	6.81	0.70
MID8	6.80	0.69	6.81	0.69
MID12	6.16	0.65	6.17	0.66
SUM06	3,391	0.65	3,392	0.65

[a] The five covariates were elevation, population density, relative humidity, temperature, and wind speed.

Table 10. Standard Deviations of Residuals (Errors) of Ozone Estimation in the California and NY/NJ/CT Areas by the Regression and Kriging Methods

Area	Kriging	Regression
California	15.32	21.33
NY/NJ/CT	11.57	12.44

that interpolation errors do not increase (and may diminish slightly) as distance between sites increases and as one moves along an urban-to-rural gradient.

We explored kriging as an alternative to the four methods described above using data from two regions: California and NY/NJ/CT. Models were fit using two thirds of the data from each region, and then tested on the remaining one third. Results are given in Table 10. Interpolation errors (i.e., SDs) were somewhat larger in general than those obtained for the country as a whole. This may relate to the regions analyzed, which have some of the highest and most variable ozone concentrations in the country, or to the small sample sizes and the two-stage validation method employed. For these data subsets, the kriging method performed better than the regression method, suggesting that distance-based approaches have merit. This should be further investigated in future work.

RELIABILITY OF THE ACTIVITY HISTORY QUESTIONS

Fifty-two Yale freshmen (30 females and 22 males) completed the activity history questions on two separate occasions approximately one month apart. The mean subject age was 19 (range 17 to 21). Response frequencies are displayed in Table 11 and in Figures 9–13. Almost half of the subjects

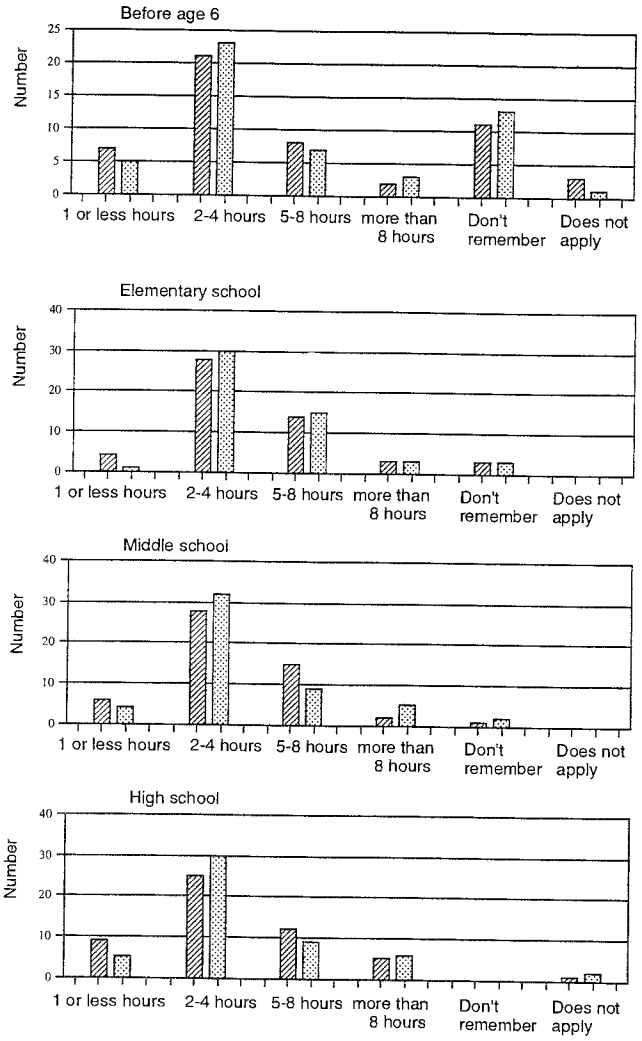


Figure 9. Number of days per week spent in typical outdoor physical activities during the nine-month academic year. Distribution of answers on test (hatched bars) and retest (stippled bars) for four life epochs.

reported participating in outdoor physical activities (question 39) most days during the academic year (September through May); progressively fewer subjects reported participating in outdoor activities 3 to 4 days/week, 1 to 2 days/week, and never. There were no obvious trends over life epochs in the distribution of outdoor activity days, except that more students reported "Don't remember" in the period before age 6. Exertion levels for outdoor activities during the academic year (question 40) varied over life epochs; there was a monotonic shift toward greater reporting of strenuous activities as the subjects aged. For example, although only 5 test subjects reported strenuous activity before 6 years of age, 27 subjects reported strenuous activity during the high school years. This same trend was seen in the data on summer activity levels (question 43). Whether these trends reflect real changes in activity levels over life epochs, or simply reflect differential recall, is not clear. Summer participation in outdoor physical activities (question 41) showed a similar distribution to that during the academic year, except that slightly more students reported

Table 11. Numbers of Responses to Activity History Questions at Test and Retest Among 52 Yale University Freshmen[a]

Question	Choices	Before Age 6		Elementary School		Middle School		High School	
Academic Year (Sept – May)									
39. On average, how many days each week did you participate in outdoor physical activity?	Never	4	1	3	0	4	1	4	3
	1–2 days/week	12	8	8	4	6	7	6	11
	3–4 days/week	6	15	16	16	18	22	20	18
	Most days	24	19	24	29	24	22	22	20
	Don't remember	6	9	1	3	0	0	0	0
40. How would you describe the outdoor activities noted above in terms of physical exertion (check all that apply).	Light	14	10	10	1	9	5	6	8
	Moderate	22	22	29	31	23	27	16	19
	Strenuous	5	8	10	16	19	19	27	24
	Don't remember	9	10	2	3	0	0	0	0
	Does not apply	2	2	1	1	1	1	3	1
Summer (June – Aug)									
41. On average, how many days each week did you participate in outdoor physical activities?	Never	2	0	1	0	1	0	2	3
	1–2 days/week	7	3	7	3	7	5	13	8
	3-4 days/week	8	13	11	14	14	19	12	19
	Most days	26	25	32	34	30	28	25	22
	Don't remember	9	11	1	1	0	0	0	0
42. On a typical outdoor activity day, how many hours did you spend doing these activities?	1 hour or less	7	5	4	1	6	4	9	5
	2–4 hours	21	23	28	30	28	32	25	30
	5–8 hours	8	7	14	15	15	9	12	9
	More than 8 hours	2	3	3	3	2	5	5	6
	Don't remember	11	13	3	3	1	2	0	0
	Does not apply	3	1	0	0	0	0	1	2
43. How would you describe the outdoor activities noted above in terms of physical exertion (check all that apply).	Light	13	10	10	3	8	3	8	3
	Moderate	21	21	27	31	28	31	16	23
	Strenuous	6	10	13	15	16	18	27	25
	Don't remember	9	10	2	3	0	0	0	0
	Does not apply	3	1	0	0	0	0	1	1

[a] For each life epoch, the left column gives the number of responses at the first test, and the right column the number of responses at the retest. All questions refer to the years before coming to Yale.

outdoor activity on "most days" during the summer season than during the academic year. The time per day spent outdoors during the summer (question 42) was most frequently reported as two to four hours, and did not appear to vary over life epochs.

Examination of Figures 9–13 conveys a general impression of consistency in the answer distributions between test and retest. However, an unexpected and apparently systematic trend away from the lowest category of activity duration and intensity is evident in comparing test and retest results. The interpretation of this trend is unclear.

Overall reliability was assessed using the simple and weighted kappa statistic. A kappa of 0 indicates no agreement beyond that which would be expected by chance alone. A kappa of 1.0 represents perfect agreement. Intermediate values represent varying levels of agreement above

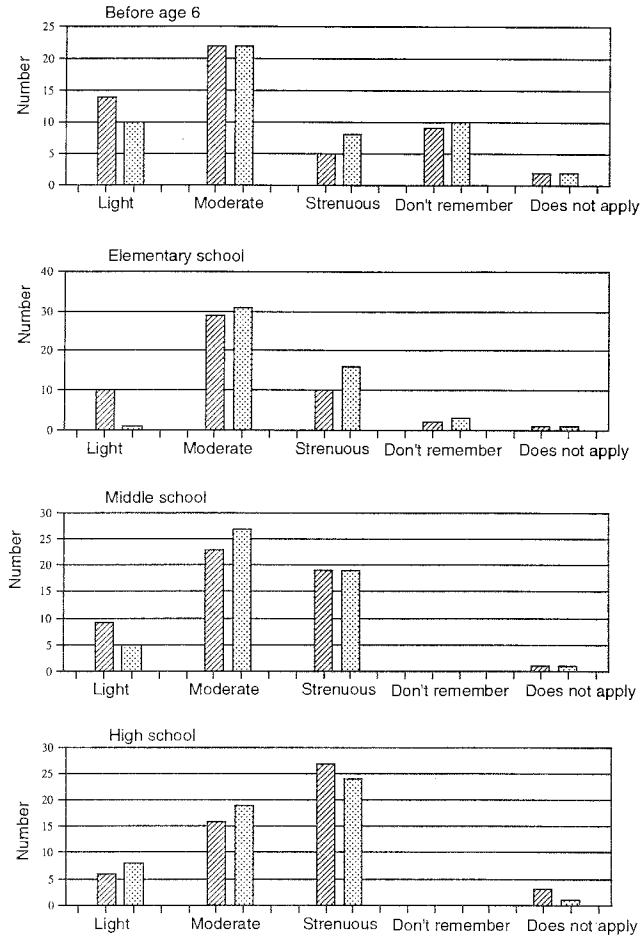


Figure 10. Typical outdoor physical activity levels during the nine-month academic year. Distribution of answers on test (hatched bars) and retest (stippled bars) for four life epochs.

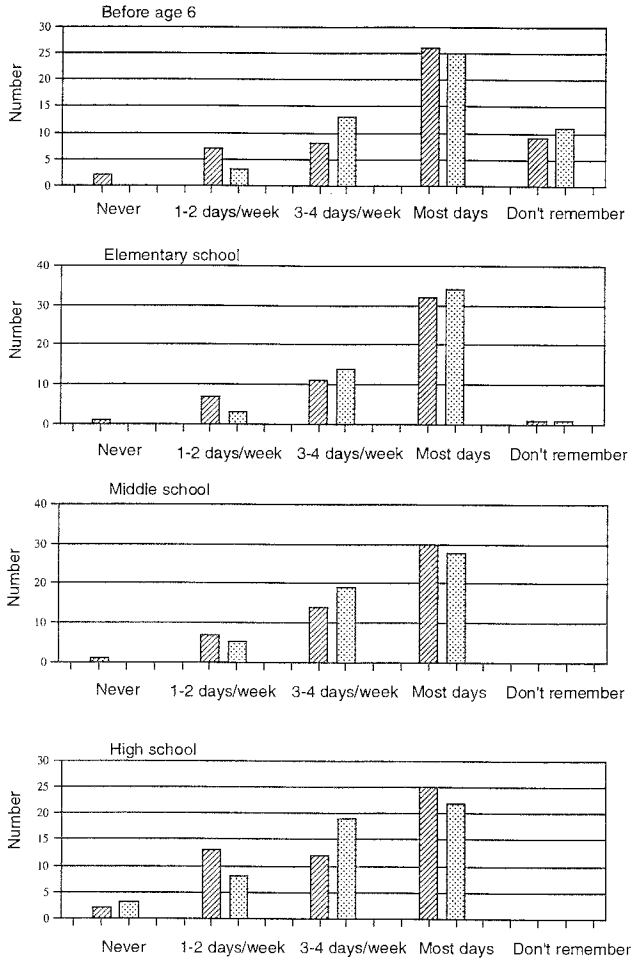


Figure 11. Number of days per week spent in typical outdoor physical activities during the three summer months. Distribution of answers on test (hatched bars) and retest (stippled bars) for four life epochs.

that due to chance. Landis and Koch (1977) consider values between 0.21 and 0.40 as fair, values between 0.41 and 0.60 as moderate, and values between 0.61 and 0.80 as substantial agreement. Although the rationale for these designations was somewhat arbitrary, they provide a framework for interpretation that has been used widely in previous studies. Table 12 presents the kappa statistics associated with 20 activity history questions (five questions for each of four life epochs). Simple kappas ranged from 0.20 to 0.57. Weighted kappas ranged from 0.24 to 0.66. Most of the observed kappas fell in the range that Landis and Koch (1977) would characterize as fair to moderate agreement. There were no obvious trends in the kappa statistics over the four life epochs.

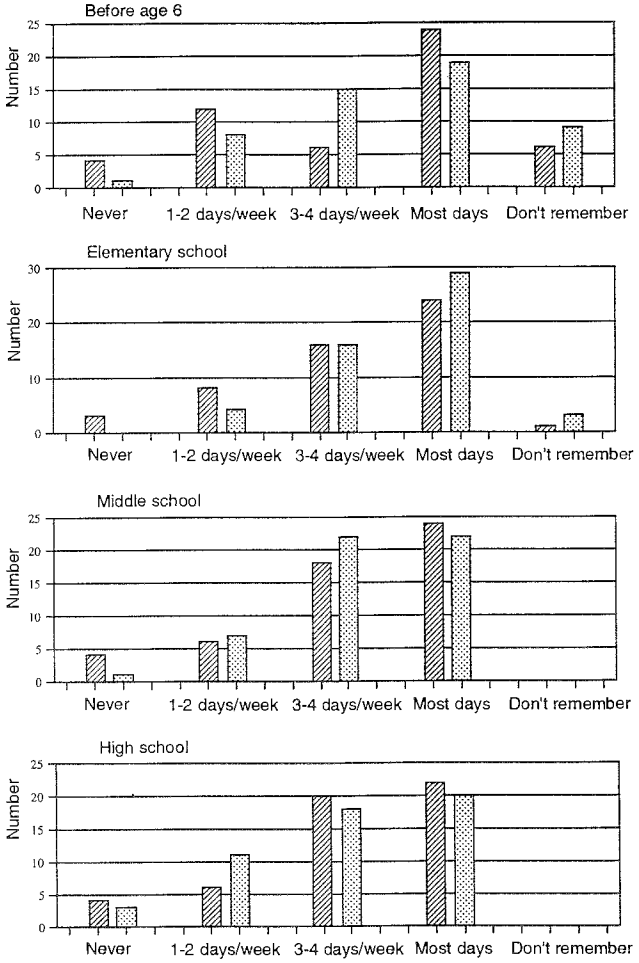


Figure 12. Number of hours per day spent in typical outdoor physical activities during the three summer months. Distribution of answers on test (hatched bars) and retest (stippled bars) for four life epochs.

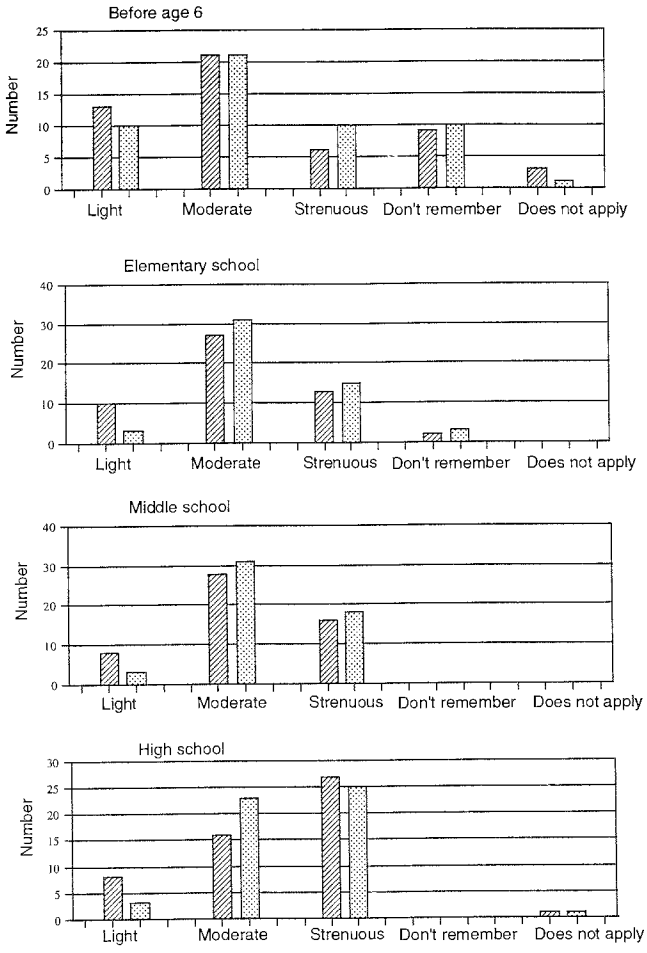


Figure 13. Typical outdoor physical activity levels during the three summer months. Distribution of answers on test (hatched bars) and retest (stippled bars) for four life epochs.

LONG-TERM EXPOSURE ESTIMATION

Figure 14 is a map showing the places of residence for the 200 Yale University freshmen for whom we developed 10-year ozone exposure estimates. Locations where more than one subject lived are indicated by multiple dots extending horizontally to the right from the town of residence. It is interesting that the residential distribution of this sample qualitatively resembles the distribution of monitoring site locations (Figure 2). Figure 15 is a histogram of the 10-year average ozone exposure estimates obtained by the time-dependent estimation method (the picture for the time-independent method is not shown but was quite similar). Table 13 shows summary statistics for the distributions of long-term exposures for the time-independent and time-dependent exposure methods. Other than a tendency for exposures from the time-dependent method to congregate more tightly in the center of the distribution, the two distributions do not differ greatly.

Results of a nested random effects analysis of variance on the annual exposure estimates from the time-dependent

Table 12. Percentage of Test and Retest Agreement and Kappa Statistics for Physical Activity Pattern

Question	Method	Before Age 6	Elementary School	Middle School	High School	Mean ± SE
Academic Year (Sept-May)						
39. On average, how many days each week did you participate in outdoor physical activities?	% of agreement	61.5	61.5	59.6	65.4	62.0 ± 2.4
	Simple kappa	0.481	0.390	0.370	0.487	0.43 ± 0.06
	Weighted kappa	0.571	0.401	0.406	0.582	0.49 ± 0.10
40. How would you describe the outdoor activities noted above in terms of physical exertion?	% of agreement	59.6	51.9	65.4	73.1	62.5 ± 9.0
	Simple kappa	0.439	0.201	0.442	0.572	0.41 ± 0.16
	Weighted kappa	0.498	0.243	0.434	0.550	0.43 ± 0.13
Summer (June-Aug)						
41. On average, how many days each week did you participate in outdoor physical activities?	% of agreement	63.5	71.2	65.4	57.7	64.5 ± 5.6
	Simple kappa	0.458	0.457	0.399	0.370	0.42 ± 0.04
	Weighted kappa	0.457	0.523	0.489	0.523	0.50 ± 0.03
42. On a typical outdoor activity day, how many hours did you spend doing these activities?	% of agreement	57.7	65.4	67.3	67.3	64.4 ± 4.6
	Simple kappa	0.422	0.426	0.460	0.500	0.45 ± 0.04
	Weighted kappa	0.520	0.434	0.569	0.565	0.52 ± 0.06
43. How would you describe the outdoor activities noted above in terms of physical exertion?	% of agreement	61.5	65.4	63.5	57.7	62.0 ± 3.3
	Simple kappa	0.475	0.428	0.352	0.301	0.39 ± 0.08
	Weighted kappa	0.658	0.516	0.424	0.343	0.49 ± 0.14
Mean (SE)	% of agreement	60.8 (2.2)	63.1 (7.1)	64.2 (2.9)	64.2 (6.6)	
	Simple kappa	0.46 (0.03)	0.38 (0.10)	0.40 (0.05)	0.45 (0.11)	
	Weighted kappa	0.54 (0.08)	0.42 (0.11)	0.51 (0.10)	0.51 (0.10)	

Figure 14. Map of the places of residence for the 200 Yale University freshmen for whom 10-year ozone exposure estimates were developed. In locations with multiple subjects, a series of dots extends horizontally to the right of the location.

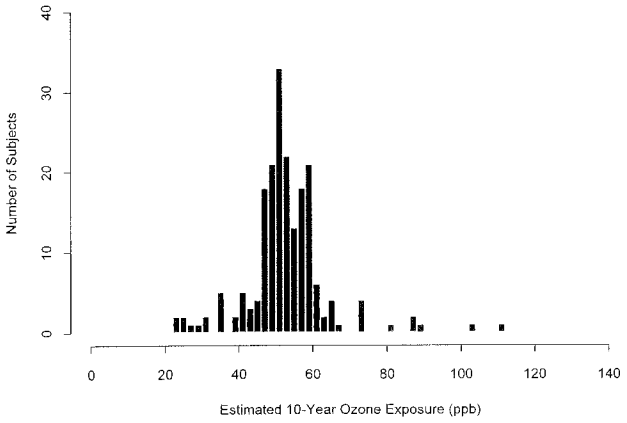


Figure 15. Histogram of the 10-year average ozone exposure estimates obtained by the time-dependent method, based on annual, individual estimates.

Table 13. Summary Statistics of the Distribution of Long-Term Individual Ozone Exposure Estimates (in ppb) Obtained by the Time-Independent and Time-Dependent Methods

	Time-Independent Method (n = 199)	Time-Dependent Method (n = 196)
Mean	51.41	52.73
SD	12.47	11.16
Variance	155.42	124.53
Maximum	111.07	110.97
95th percentile	66.67	72.12
75th percentile	56.68	57.66
Median	51.32	51.83
25th percentile	45.11	48.41
Minimum	21.4	22.38

method are displayed in Table 14. This analysis partitions the observed variance into two components, within-subject and between-subject. The between-subject variance (121.7 ppb^2) was approximately 2.4 times larger than the within-subject variance (50.1 ppb^2). For comparison, the interpolation error variance for the regression method (i.e., the square of the MAX8 residual SD displayed in Table 6) was 46.2 ppb^2.

QUALITY ASSURANCE

To assess quality control methods in use at ozone monitoring sites, we administered a questionnaire by telephone to agency personnel responsible for air monitoring at 60 sites in 25 states across the United States. Data on four key variables are presented in Table 15. All but one site used state-of-the-art ultraviolet photometric instruments. The remaining site used the older, but accurate, ethylene gas method. Instrument audits by an outside agency occurred quarterly (the recommended frequency) at 28 sites, semiannually at 12 sites, and only yearly at 20 sites. Filters were changed weekly at 19 sites, biweekly at 37 sites, and monthly at 4 sites. An inline filter becomes dirty if not changed every two weeks, and a dirty filter can serve as an ozone sink. At 48 of the 60 sites, calibrations are routinely performed through the sample line and filter. At the remaining 12 sites, calibration gas was reported to be delivered directly to the instrument. The latter procedure may in some cases negatively bias subsequent ozone data. This may occur because ambient air must pass through the sample line and filter, where a portion of the ozone may react and be removed before measurement. This effect can be avoided by performing calibrations through the sample line. These results suggest that appropriate quality control procedures were being followed at the majority of ozone monitoring sites, but compliance with recommended procedures was not complete in this sample.

Table 14. Variance Components Analysis Examining the Between- and Within-Subject Variability in Individual Ozone Exposure Estimates (Time-Dependent Method) Based on a Nested Analysis of Variance

Source	Variance (ppb^2)
Between subjects (space)	121.7
Within subjects (time)	50.1
Interpolation error[a]	46.2

[a] Estimate based on square of SD of residuals by interpolation to the three nearest monitoring sites, using a regression-based model.

Table 15. Summary of Responses to Questions About Key Quality Control Procedures at 60 Ozone Monitoring Sites

Variable	Answer	Number of Sites (%)
Monitor type	UV photometer	59 (98)
	Ethylene gas	1 (2)
Instrument audits	Quarterly	28 (47)
	2/year	12 (20)
	1/year	20 (33)
Inline filter changes	Weekly	19 (32)
	Biweekly	37 (62)
	Monthly	4 (6)
Calibration site	Sample line	48 (80)
	Instrument	12 (80)

DISCUSSION

The purpose of this study was to develop and evaluate methods that utilize nationwide ozone monitoring data to estimate long-term ozone exposures of people living in the United States. If the available data were sufficiently rich, spatial variations sufficiently smooth, and methods sufficiently convenient and reliable, then a new generation of epidemiologic studies with more precise, reliable, and powerful exposure measures would be made feasible.

Whether or not humans experience adverse respiratory effects following long-term ozone exposures is one of the major remaining uncertainties regarding ozone health effects. Long-term studies have demonstrated that adverse effects do occur in animals (Tyler et al. 1988). Human clinical studies have observed acute inflammatory changes in the lungs of young adults following brief ambient-level ozone exposures (Devlin et al. 1991). With repeated exposures over several days, indications of acute inflammation (such as neutrophil influx) diminish while evidence of ongoing cell damage remains (Folinsbee et al. 1994; Kinney et al. 1996). However, the long-term respiratory consequences of repeated inflammatory events, especially for the developing lung, are unknown.

Past epidemiologic work addressing the respiratory effects of long-term ozone exposures has been hampered by difficulties of exposure assessment. These difficulties have mainly involved the lack of feasible methods for obtaining

and combining the data necessary to derive reliable long-term exposure estimates. Exposure assignments have usually been limited in temporal and geographic scope. Exposure histories have seldom extended back over more than a small fraction of the full period of exposure likely to be relevant to chronic respiratory effects; most studies have in fact used only an annual average to represent the long-term exposure profile of a subject or study area. Because of limitations in the spatial extent of air monitoring in the past, most studies have been limited to those geographic areas with relatively extensive measurements or else have undertaken expensive, specialized monitoring in a small number of locations in support of the study. The advent of the AIRS data base in the 1980s, with its extensive, computerized air monitoring records, made a new generation of epidemiologic studies possible. However, utilization of this resource has been hindered by the lack of methods for deriving from it estimates of population exposures. Barriers to fuller use of these data have included computational difficulties inherent with large data sets as well as the lack of a conceptual framework of, and straightforward methods for, translating these monitoring data into space- and time-referenced exposure histories of individuals. The present study focused on developing tools that may overcome some of the above-mentioned problems.

INTERPOLATION OF OZONE CONCENTRATIONS

Errors associated with interpolation of long-term average ozone concentrations did not vary markedly across four nearness-based interpolation methods. Interpolation errors diminished as a function of the number of nearby sites used in the model, up to three sites, but then either increased, or diminished only slightly, as more sites were added to the model. For the country as a whole, the regression method slightly outperformed the others regardless of the number of nearest sites used. The results of this work suggest that interpolations of long-term average ozone concentrations between available U.S. monitoring sites using a simple regression on the three nearest sites yielded reasonably precise exposure estimates. For the MAX1 metric, an error SD of 7.9 ppb was observed, which amounted to 13% (coefficient of variation) of the overall mean concentration. Similar results were obtained for the other ozone metrics except for SUM06, which had a coefficient of variation of 44%. Interpolation errors were largest for areas where concentrations were highest, for example, in southern California. Including covariates such as weather factors, population density, and elevation did not substantially improve the model fits.

Interpolation methods for estimating values of a spatial variable at unmeasured locations are important tools in environmental research. Abbey and colleagues (1991b) applied an inverse-distance–squared method to the three nearest sites to impute ozone concentrations at zip code centroids in a study of air pollution health effects in Southern California. A similar approach was used recently by Künzli and colleagues (1997) in a pilot study in a similar geographic area. Neither study reported estimation errors in a way comparable to our approach, nor did they compare the inverse-distance–squared method to other interpolation schemes. Abbey and coworkers (1991b) reported correlations ranging from 0.63 to 0.92 between estimated and observed two-year ozone means, depending on the ozone metric used. In our study, regression on the three nearest ozone monitoring sites yielded an R^2 of 0.74, corresponding to a correlation of 0.86.

Kriging has been applied extensively for estimating long-term ozone exposures in agricultural impact studies (Lefohn et al. 1987); it was also applied in a recent study of spatial variations in ambient ozone concentrations in metropolitan Toronto (Liu and Rossini 1996). In the study by Lefohn and colleagues, kriging consistently underestimated actual ozone values at rural sites at the high end of the concentration distribution, and appeared to overestimate low values. In their Toronto study, Liu and Rossini developed a kriging model using continuous ozone data from a set of government-operated sites; the model was then used to predict ozone at a series of residential locations for which outdoor measurements were obtained using the passive Koutrakis sampler (Koutrakis et al. 1993). Their kriging model consistently overestimated the measured ozone levels at the residences, which the authors interpreted as evidence that the government ozone monitoring sites were biased toward higher values. However, the extent to which the observed differences may have been due to the different methods used for sampling at the two types of sites is not clear. The authors reported that kriging performed better than a simple nearest-neighbor approach (that is, prediction of residential ozone concentration using the nearest fixed-site monitor).

Wartenberg and coworkers (1991) presented results of a simulation study comparing three spatial methods applied to groundwater contamination and the effects of spatial interpolation errors on a hypothetical case-control study. The three estimation methods were nearest-neighbor, inverse-distance–squared average, and ordinary kriging. The latter two methods yielded similar results, and both appeared to outperform the nearest neighbor method. Because

of its conceptual and computational simplicity, the inverse-distance–squared method was viewed as preferable to kriging by the authors.

Laslett (1994) presented an empirical comparison of kriging and spline methods applied to several spatial data sets, finding that kriging always performed as well as or better than splines in terms of the mean squared error of prediction. To our knowledge, no one has previously used a simple regression-based approach to the spatial interpolation of air pollution data. In exploratory analyses in our study, a kriging approach appeared to outperform the regression method using data from California or from the three-state region NY/NJ/CT. Distance-based interpolation methods like kriging should be further investigated in future work.

That interpolation errors were highest in southern California was not surprising. Sites in the South Coast Air Basin of California consistently yield the highest and most variable ozone concentrations in the nation. Mountainous geography and prevailing west-to-east summer winds lead to large contrasts in concentrations across the basin. Our methods were simple in that they identified relevant predictor sites solely on the basis of ranked distance from the index site. We did not incorporate information on geographic barriers between sites or on prevailing wind fields. Methods that incorporate such information (U.S. Environmental Protection Agency 1977; Abbey et al. 1991b) may reduce estimation errors, at the expense of increases in model complexity and data base requirements.

Our initial attempts to augment the simple ozone interpolation methods with covariates did not substantially improve long-term ozone estimates. This was somewhat surprising. The covariates were population density, temperature, wind speed, and relative humidity in the area surrounding ozone sites, as well as site elevation. The dynamics of tropospheric ozone formation and destruction are well established (National Research Council 1991; Finlayson-Pitts and Pitts 1993). Ozone forms via photochemical reactions involving nitrogen oxides (NO_x) and reactive hydrocarbons (HC). Greater solar intensities and higher temperatures enhance its production. Because motor vehicle and other anthropogenic combustion sources are important contributors to NO_x and HC emission densities, the spatial distribution of these densities is expected to parallel that of population density. Given these ozone dynamics, it seems reasonable to expect that population density and meteorologic conditions would relate to ambient ozone concentrations.

We found that, at least for simple linear predictions of long-term ozone averages, these covariates lacked explanatory power once concentrations from nearby ozone sites were taken into account. Similar results were reported in a study that augmented kriging-based ozone interpolation models with data on traffic density in metropolitan Toronto (Liu and Rossini 1996). It is worth noting that in our approach, covariates were added as independent linear predictors in a multiple regression. The influences of covariates may be nonlinear, or involve interactions with one another or with upwind ozone concentrations. For example, we know that ozone can react with NO_x if excess NO_x are present. As a result, ozone concentrations are often lower in urban cores than in outlying areas where NO_x emission densities are lower. One approach would be to utilize wind rose estimates (i.e., the distribution of wind direction and wind speed) at site locations to weight the interpolations. Another would be to use complex nonlinear approaches such as neural nets.

ACTIVITY HISTORY QUESTIONS

The temporal pattern of ambient ozone concentrations in the areas where people spend time is the basis of their exposure level. However, the impact of ambient concentrations on individual exposures and received doses depends on other factors such as local traffic density, local tree canopy density, the fractional penetration of ambient ozone into individual homes (influenced by ventilation factors such as air conditioner use), indoor decay rate (influenced by surface-to-volume ratio, indoor surface coverings, and indoor sources such as gas stoves), the fraction of time individuals spend outdoors, and individuals' levels of physical exertion (Contant et al. 1987; Weschler et al. 1989; Hayes 1991; Liu et al. 1993, 1995). Because of the importance of these factors, it is possible that sedentary individuals living in areas with high ambient ozone concentrations would receive lower long-term ozone doses than active individuals living in areas with moderate ambient concentrations. An ideal estimator of individual ozone exposure (or dose) would take into account ambient concentrations as well as all the factors that modify individual exposure and dose. The value of this approach would lie in its power to assign accurately a range of individual exposure or dose estimates to study subjects.

One objective of the present study was to address in a limited way the possibility that usable information on factors that modify long-term dose can be obtained by administering recall questionnaires to young adults. The work presented here focused on only two relevant factors: outdoor activity times and intensities. We built on past work, especially that of Tager and colleagues (see Part II of this Research Report, and Künzli et al. 1996), by developing a questionnaire that posed activity questions within four specific life periods, or epochs. Justifications for this par-

ticular method of time reference include the likelihood that young adults remember activity events within school epochs, that participation in organized sports differs to some extent across school epochs, and that splitting exposure into a consistent set of four periods for all subjects facilitates testing of health effects hypotheses involving exposures at different ages and stages of lung development.

When the test was administered two times approximately one month apart to a set of 52 Yale freshmen, a fair to moderate level of agreement between test and retest was observed in answers to the activity questions. The reliability coefficients (kappa statistics) exhibited no obvious trends over life epochs. The relatively short time interval (one month) between test and retest may have introduced a positive bias in the reliability estimates if subjects were able to remember and reproduce their test responses. Overall, these results are somewhat disappointing. Whether retrospective questionnaire data can be used effectively to modify individual exposure estimates in ways that reduce misclassification remains to be determined. Several important issues will need to be studied before more definitive conclusions can be drawn, including the relation between the reliability and the validity of these questions, a statistical assessment of what level of reliability is considered adequate, identification of the sources of error that limit reliability, and the possibility that reliability could be improved by considering other aggregates of data.

Reliability addresses only the consistency over time in the subject's answers to activity history questions, rather than the veracity or "validity" of the responses. The latter would require a "gold standard" against which the subject's answers could be compared. No gold standard is available for the activity questions we evaluated in this study. In particular, it is not clear that parental recollections of children's activity patterns would be more valid than those of the children themselves. If the activity history answers obtained in our study were valid, they should also be reliable (i.e., consistent) on repeated testing. Thus, good reliability is consistent with, but does not prove, validity.

Künzli and coworkers reported results of a closely related, but far more extensive study evaluating a retrospective questionnaire given in a test-retest format to a group of 175 freshmen at the University of California, Berkeley (see Part II of this Research Report, and Künzli et al. 1996). As noted above, their activity questions were residence-specific rather than epoch-specific. In addition, their retest took place within five to seven days of the test, as compared with the one-month gap in our study. Further, in their reliability analysis, they often collapsed cells to yield dichotomous outcomes for analysis. Although these factors limit the direct comparability of results, many of their results are relevant to the present discussion. For example, in examining data from subjects with multiple residences, they too observed no apparent trends in kappa statistics over time. Like us, they observed a higher prevalence of "Don't remember" on questions addressing levels of outdoor activities early in life as compared with later in life. Künzli and colleagues (1996, p. 309) concluded that "retrospective lifetime activity assessment is feasible and that our questions have the same degree of reliability found for other measures that are often used in epidemiological research."

LONG-TERM EXPOSURE ESTIMATION

We applied the regression interpolation method, in conjunction with residential histories, to estimate retrospective 10-year ozone exposure histories of 200 Yale freshmen. The algorithm we developed provides a relatively simple approach for estimating long-term exposures in nationwide samples of young people. Although our data base was limited to the years 1981 through 1990, this record could be extended fairly readily to more recent years (as well as to several previous years) so that lifelong exposure estimates could be computed for college-age cohorts. Analysis of the variance components showed that variations in exposures between subjects exceeded both variations within subjects (i.e., over time) and variations due to error by more than a factor of 2.

STUDY LIMITATIONS

By estimating long-term ozone concentrations at ozone monitoring sites and then comparing the estimated and observed values, we tested and compared interpolation methods. Our objective was to determine the quality of interpolations at residential locations of hypothetical study subjects. Our approach assumed that monitoring sites were representative of residence locations, in the sense that the errors of interpolation to monitoring sites were similar in magnitude to those that would occur at residences, if such data were available. We did not test the validity of this assumption; however, it seems reasonable in that most ozone monitoring sites are located in residential areas. Furthermore, the spatial density of monitoring sites seems to parallel that of population density and of the home residential locations of a sample of Yale students (Figures 2 and 14). One way this issue could be evaluated would be to restrict the interpolation to only those sites that are labeled as being in residential areas. Standard errors of estimation could then be compared with the results obtained for the full set of sites.

The regression method performed slightly better than the other interpolation methods we evaluated. However, the

regression model was fit using all 1,112 sites, and then the residuals were used to assess estimation errors. The other interpolation methods were all based on local estimation; that is, only the nearest n sites were used to estimate ozone at the index site. A fairer way of evaluating the regression method would have been to fit the model 1,112 separate times, excluding a different index site before fitting the model in each case. It also would be interesting to include and compare several other interpolation methods, such as locally fitted regression (for example, LOESS) and splines.

Another limitation of the approach used to date is that it ignores the pattern of missing ozone data. Not all of the 1,112 ozone sites used in the analysis were in operation for the full 10 years. In general, in any given year, fewer than 700 sites were in operation. Further, we limited our attention to summer ozone data. This seems justified given that maximal concentrations occur then. However, substantial exposures may occur during the spring and fall in some locales. Extending our analysis to other seasons would be difficult because ozone is often not monitored year-round. To address problems of missing data, the completeness of data at each site could be used as a weighting factor in the interpolation model. Alternatively, sites used in interpolation could be restricted to a subset that meets a completeness criterion. We intend to explore these methods in subsequent analyses.

STUDY DESIGN IMPLICATIONS

Considering our results as a whole on the spatial and, to a lesser extent, temporal distributions of nationwide ozone concentrations and exposures, what broad conclusions can be drawn about the adequacy of the available ozone data for long-term exposure estimation? In our view, the spatial density of monitoring in the United States appears to be generally adequate for this purpose. This conclusion has several bases. Examination of intersite differences in ozone concentrations (Figure 1) showed that spatial variations are not a strong function of the distances between pairs of nearest-neighbor sites. Furthermore, interpolation errors did not increase as a function of distance when the data were split into three subsets of increasing intersite distance. These initially counterintuitive results may be explainable by the fact that monitoring site density is correlated with ozone concentrations (and variations). That is, the monitoring network is denser in urban areas where ozone is high and variable (e.g., California's South Coast Air Basin) than in rural areas where levels are lower and less variable (e.g., the Great Plains). These results reinforce the adequacy of the spatial density of monitoring sites for capturing both local and regional variations in outdoor concentrations. Further, where monitoring exists, temporal coverage is extensive (i.e., providing continuous hourly values) during at least the season of highest ozone concentrations, and often for the entire year.

Our analysis of spatial and temporal variations in individual long-term exposure estimates extends these conclusions further. In a group of 200 Yale freshmen, retrospectively estimated 10-year exposure histories exhibited between-subject variation that was over twofold higher than both the within-subject (temporal) and error variations. These results imply that between-subject variations (driven mainly by spatial variations in ambient levels) are measurable using the methods we have developed.

Given the observed level of spatial variation in long-term ozone concentrations across the United States in this study, it is possible to compute the sample size that would be required to detect, with 80% probability, an effect on human lung function of a given magnitude in a hypothetical nationwide epidemiologic study. This exercise was carried out for forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25\%-75\%}$) using data reported by Künzli and coworkers (1997). The slope relating $FEF_{25\%-75\%}$ to long-term ozone exposure in that study was –0.021 L/sec/ppb. The residual SD of lung function was taken as the average of the male and female values reported in the study (0.985 L/sec). The variance of long-term ozone concentrations was taken as 173 ppb^2, which was the variance of interpolated MAX1 ozone in our study.

Given these assumptions, the sample size necessary to detect an effect of long-term ozone exposure on $FEF_{25\%-75\%}$ is 99. That is, if 99 people were chosen at random from the national distribution of long-term ozone exposure concentrations, there would be an 80% chance of detecting a statistically significant effect of ozone on $FEF_{25\%-75\%}$. This number should be viewed as a rough preliminary estimate because it depends on the validity of the assumptions and input values we have used. For example, we have assumed that the spatial variance in ozone concentrations across monitoring sites is representative of the variance in exposure levels across people enrolled in a hypothetical epidemiologic study. We have also assumed that the point estimate for lung function effects reported by Künzli and coworkers (1997) represents the true effect size. Also note that our analysis does not incorporate exposure or dose modifiers (e.g., activity patterns and levels), which have the potential to further disaggregate individual exposures (increasing the variance of ozone exposure) and reduce sample-size requirements.

CONCLUSIONS AND SUGGESTED AREAS FOR FUTURE RESEARCH

Several conclusions can be drawn from our study:

1. The spatial density of available ozone monitoring appears to have been adequate to capture the bulk of the local and regional spatial variations in long-term ozone concentrations across the United States during the period 1981 through 1990.
2. Although further refinements are possible, simple interpolation methods yield good estimates of long-term ozone concentrations throughout the country. A simple regression-based interpolation on the three nearest sites produced consistently good results. This implies that exposure assessment should not be viewed as an obstacle to nationwide cross-sectional epidemiologic studies addressing the respiratory effects of long-term ozone exposures in young adults. Indeed, the AIRS data base is an outstanding resource for lifetime exposure assessment in this age group.
3. Factors that modify subjects' individual exposures and doses (for example, outdoor activity time periods and levels) were assessed with fair to moderate reliability using activity history questions in a health study questionnaire administered to Yale freshmen. The feasibility of using this information to refine individual exposure or dose estimates remains to be determined.

Further work is warranted in the following areas:

1. Refinements of the interpolation models should be explored. Locally weighted regression (for example, LOESS) and splines are two approaches that should be evaluated. Also, more complex strategies for modeling the influence of increasingly available covariates may result in smaller interpolation errors. Distance-based interpolation methods such as kriging should be investigated further.
2. Methodologic work is needed to determine optimal strategies for incorporating data on individual activities and residence characteristics into long-term exposure or dose estimates.
3. The interpolation methods developed in the present study should be extended to the estimation of long-term inhalable particle concentrations. This is feasible at present for particulate matter less than 10 μm in diameter (PM_{10}), for which extensive monitoring data exist starting in 1988. In several years, the methods could be further extended to particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), once data begin to accumulate following the establishment of a National Ambient Air Quality Standard for $PM_{2.5}$) in 1998.

ACKNOWLEDGMENTS

The authors wish to acknowledge the valuable assistance of Dr. Kazuhiko Ito (New York University) in the development of the ozone data base. We also acknowledge the work of Michael Shnaidman (Columbia School of Public Health), who assisted in applying the interpolation methods to the nationwide ozone data base. John Gorczynski (New York University) carried out the telephone audit of ozone site operations. Finally, we thank the U.S. Environmental Protection Agency for providing access to the AIRS data base.

REFERENCES

Abbey DE, Mills PK, Petersen FF, Beeson WL. 1991a. Long term ambient concentrations of total suspended particulates and oxidants as related to incidences of chronic disease in California Seventh-Day Adventists. Environ Health Perspect 94:43–50.

Abbey DE, Moore J, Petersen F, Beeson L. 1991b. Estimating cumulative ambient concentrations of air pollutants: Description and precision of methods used for an epidemiological study. Arch Environ Health 46:281–287.

Contant CF, Stock TH, Buffler PA, Holguin AH, Gehan BM, Kotchmar DJ. 1987. The estimation of personal exposures to air pollutants for a community-based study of health effects in asthmatics: Exposure model. J Air Waste Manage Assoc 37:587–594.

Cressie N. 1989 Geostatistics. Am Stat 43:197–202.

Detels R, Tashkin DP, Sayre JW, Rokaw SN, Coulson AH, Massey FJ, Wegman DH. 1987. The UCLA population studies of chronic obstructive respiratory disease. Chest 92:594–603.

Devlin RB, McDonnel WF, Mann R, Becker S, House DE, Schreinemachers D, Koren HS. 1991. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. Am J Respir Cell Mol Biol 4:72–81.

Finlayson-Pitts BJ, Pitts JN Jr. 1993. Atmospheric chemistry of tropospheric ozone formation: Scientific and regulatory implications. Air Waste 43:1091–1100.

Fleiss JL. 1981. Statistical Methods for Rates and Proportions. John Wiley & Sons, New York, NY.

Folinsbee LJ, Devlin RB, Koren HS. 1994. Time course of pulmonary response to repeated ozone exposure in man. Am J Respir Crit Care Med 149:A151.

Hayes SR. 1991. Use of an indoor air quality model (IAQM) to estimate indoor ozone levels. J Air Waste Manage Assoc 41:161–170.

Horstman DH, Folinsbee LJ, Ives PJ, Abdul-Salaam S, McDonnell WF. 1990. Ozone concentrations and pulmonary response relationships for 6.6-hour exposures with five hours of moderate excercise to 0.08, 0.10 and 0.12 ppm. Am Rev Respir Dis 142:1158–1163.

Kinney PL, Nilsen DM, Lippman M, Brescia M, Gordon T, McGovern T, El-Fawal H, Devlin RB, Rom WN. 1996. Biomarkers of lung inflammation in recreational joggers exposed to ozone. Am J Respir Crit Care Med 154:1430–1435.

Koutrakis P, Wolfson JM, Bunyaviroch A, Froehlich SE, Kirano K, Mulik JD. 1993. Measurement of ambient ozone using a nitrite-coated filter. Anal Chem 65:209–214.

Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. 1996. Reliability of lifetime residential history and activity measures as elements of cumulative ambient ozone exposure assessment. J Expos Anal Environ Epidemiol 6:289–310.

Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. 1997. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen: Results of a pilot study. Environ Res 72:8–23.

Landis JR, Koch GG. 1977. The measurement of observer agreement for categorical data. Biometrics 33:159–174.

Laslett GM. 1994. Kriging and splines: An empirical comparison of their predictive performance in some applications. J Am Stat Assoc 89:391–405.

Lefohn AS, Simpson J, Knudsen HP, Bhumralkar C, Logan JA. 1987. An evaluation of the kriging method to predict 7-h seasonal mean ozone concentrations for estimating crop losses. J Air Waste Manage Assoc 37:595–602.

Liu LJS, Koutrakis P, Leech J, Broder I. 1995. Assessment of ozone exposures in the greater metropolitan Toronto area. J Air Waste Manage Assoc 45:223–234.

Liu LJS, Koutrakis P, Suh HH, Mulik JD, Burton RM. 1993. Use of personal measurements for ozone exposure assessment: A pilot study. Environ Health Perspect 101:318–324.

Liu LJS, Rossini A. 1996. Use of kriging and cokriging models to predict 12-h mean ozone concentrations in metropolitan Toronto: A pilot study. J Air Waste Manage Assoc 22:677–692.

National Research Council. 1991. Rethinking the Ozone Problem in Urban and Regional Air Pollution. National Academy Press, Washington, DC.

Ripley BD. 1981. Spatial Statistics. John Wiley & Sons, New York, NY.

Schwartz J. 1989. Lung function and chronic exposure to air pollution: A cross-sectional analysis of NHANES II. Environ Res 50:309–321.

Spektor DM, Thurston GD, Mao J, He D, Hayes C, Lippman M. 1991. Effects of single- and multiday ozone exposures on respiratory function in active normal children. Environ Res 55:107–122.

Tager IB. 1993. Summary of papers and research recommendations of Working Group on Tropospheric Ozone, Health Effects Institute Environmental Epidemiology Planning Project. Environ Health Perspect 101:237–239.

Tyler WS, Tyler NK, Last JA, Gillespie MJ, Barstow TJ. 1988. Comparison of daily and seasonal exposures of young monkeys to ozone. Toxicology 50:131–144.

U.S. Environmental Protection Agency. 1977. Guideline on Procedures for Constructing Air Pollution Isopleth Profiles and Population Exposure Analysis. Office of Air and Waste Management, Research Triangle Park, NC.

Wartenberg D, Uchrin C, Coogan P. 1991. Estimating exposures using kriging: A simulation study. Environ Health Perspect 94:75–82.

Weschler CJ, Shields HC, Naik DV. 1989. Indoor ozone exposures. J Air Waste Manage Assoc 39:1562–1568.

APPENDIX A. QUESTIONNAIRE

Survey 1997 ID # 3/ ___

YALE /COLUMBIA RESPIRATORY HEALTH STUDY
SURVEY QUESTIONNAIRE

SPRING 1997

Thank you for your willingness to participate in this study. Your cooperation is very important to the success of the study.

This is a questionnaire you are asked to fill out. Please answer the questions as completely and accurately as possible. **All the information obtained in the study will be kept confidential and used for research purposes only by the study team. The title page with your name on it will be removed from the rest of the questionnaire in order to ensure confidentiality. Yale University will not have access to individual data from this study.**

The questions can be answered by checking the best answer or by filling in a blank with a number or a word.

If you need assistance in answering a question, please put a check in front of the question. The study coordinator will assist you with these questions when you have completed the questionnaire.

1. NAME: _____
(First Middle Initial Last)

2. LOCAL TELEPHONE : _____

3. E-MAIL ADDRESS: _____

4. TODAY'S DATE: _____
(Month/Day/Year)

5. DATE OF BIRTH: _____
(Month/Day/Year)

TO BE COMPLETED BY STAFF:
Questionnaire reviewed by:_____ Date:_____

Height: _____Inches
Has the subject had a chest cold in the past 7 days? _____Yes _____No
If Yes, how many days since last symptoms were experienced? _____Days

Survey 1997 ID # 3/ ___

RESPIRATORY HEALTH HISTORY

These questions are concerned with your respiratory health. Please answer yes or no if applicable

6.A **Do you usually have a cough? (exclude clearing of throat)** ___Yes ___No

IF YES

		YES	NO
6.B	Do you usually cough as much as 4 to 6 times a day, 4 or more days out of the week?		
6.C	Do you usually cough on most days for 3 consecutive months or more during the year?		

7.A **Do you usually bring up phlegm from your chest?** ___Yes ___No

IF YES

		YES	NO
7.B	Do you usually bring up phlegm like this as much as twice a day, 4 or more days out of the week?		
7.C	Do you bring up phlegm like this on most days for 3 consecutive months or more during the year?		

8. **Does your chest ever sound wheezy or whistling:**

		YES	NO
8.A	When you have a cold?		
8.B	Occasionally apart from colds?		
8.C	Most days or nights?		

Survey 1997 ID # 3/ ___

9.A **Have you ever had an attack of wheezing that made you feel short of breath?**

___Yes ___No

IF YES

		YES	NO
9.B	Have you ever required medicine or treatment for the attack(s)?		

10.A **Have you ever been diagnosed by a physician as having asthma?**

___Yes ___No

IF YES

10.B	How old were you when you were first diagnosed as having asthma?	_____ Years old	
		YES	NO
10.C	Have you had any asthma symptoms during the past 12 months?		
10.D	Have you taken any prescription or over the counter medication for asthma during the past 12 months?		
10.E	Have you ever been hospitalized for asthma?		

11. **If you get a cold does it usually go to your chest? (Usually means more than half the time).**

___Yes ___No

12. **During the past three years, have you had any chest illnesses that have kept you indoors at home or in bed?**

___Yes ___No

Survey 1997 ID # 3/ ___

For each of the following diseases please tell us if you ever had the disease, if it was confirmed by a doctor, and the age at which you first had it.

	DISEASE	(A) HAD DISEASE?	(B) CONFIRMED BY DOCTOR?	(C) AGE YOU FIRST HAD
13.	Bronchitis	___Yes ___ No	___Yes ___ No	_____ Yrs old
14.	Pneumonia	___Yes ___ No	___Yes ___ No	_____ Yrs old
15.	Hay Fever	___Yes ___ No	___Yes ___ No	_____ Yrs old
16.	Allergies	___Yes ___ No	___Yes ___ No	_____ Yrs old
17.	Sinus trouble	___Yes ___ No	___Yes ___ No	_____ Yrs old
18.	Pleurisy	___Yes ___ No	___Yes ___ No	_____ Yrs old
19.	Other chest illnesses	___Yes ___ No	___Yes ___ No	_____ Yrs old
20.	Chest operations	___Yes ___ No	___Yes ___ No	_____ Yrs old
21.	Chest injuries	___Yes ___ No	___Yes ___ No	_____ Yrs old

Survey 1997 ID # 3/ _ _ _

RESIDENTIAL HISTORY

22. **Have you spent one or more continuous years living outside the United States?**
___Yes ___No

23. **List all the towns/cities you have lived in for at least one year prior to coming to Yale, starting from the most recent town/city. Count only those places you would normally call home (e.g., not counting boarding schools or Yale). Please indicate whether your neighborhood was urban, suburban or rural by circling the appropriate term for each residence.**

Town / City	State	Zip	Circle one	Dates of Residence
A (most recent)			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
B.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
C.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
D.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
E.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
F.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
G.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr
H.			Urban Suburban Rural	From: ___/___ To___/___ mo yr mo yr

Survey 1997 ID # 3/ _ _ _

The following section asks questions about the homes you lived for the three most recent towns/cities (A, B, and C) listed in the above table. If you lived in more than one home in the same town/city, choose the home you lived in the longest. Be as complete as possible, but do not guess. Use check marks to indicate your answers.

		Town/City A (Most Recent)	B	C
24. What type of heating system was used in this home? (check all that apply).	Steam or hot water			
	Forced hot air			
	Electric baseboard			
	Gas or kerosene heater			
	Other			
	None			
	Don't remember			
25. A Was an air conditioner used to cool this home in the summer months?	Yes			
	No			
	Don't remember			
IF YES, answer 25.B and 25.C				
25.B Which rooms were air conditioned? (Check all that apply).	Whole house			
	Your bedroom			
	Family/Living room			
	Other			
	Don't remember			
25.C During the summer, how often was the air conditioner used?	Never			
	Less than 14 days			
	Between 14-28 days			
	More than 28 days			
	Don't remember			
26. Was a window fan or attic fan used to cool this home in summer?	Yes			
	No			
	Don't remember			
27.A Were there any dogs, cats, other furry pets, or birds living in this home?	Yes			
	No			
	Don't remember			
IF YES				
27.B How many such pets?	1			
	2-3			
	4 or more			
	Don't remember			
28. Was a gas stove, or a gas oven used for cooking in this house?	Yes			
	No			
	Don't remember			

Survey 1997 ID # 3/ _ _ _

SMOKING

29.A **Have you ever smoked cigarettes? (No means less than 5 packs of cigarettes in your lifetime or less than 1 cigarette per day for 6 months).**
___Yes ___No

IF YES

		YES	NO
29.B	How old were you when you first started smoking cigarettes regularly?	___ Age in Years	
29.C	During the period you smoked regularly, how many cigarettes per day did you smoke on average?	___Cigarettes per day	
29.D	Do you now smoke cigarettes?		

30. **Have you smoked at least 20 cigars in your entire life?** ___Yes ___No

31. **Have you ever smoked at least 20 pipefuls of tobacco in your entire life?**
___Yes ___No

32. **Have you ever regularly used other smoking products?** ___Yes ___No

Survey 1997 ID # 3/ _ _ _

33. **Did anybody smoke regularly in your home while you were growing up?**
___Yes ___No

IF YES

Complete the following table:

	Did this person smoke in your home?			Number of cigarettes per day this person smoked in your home				Your age when this person smoked in your home		
	Yes	No	Don't Recall	0-10	11-20	>20	Don't recall	0-6	7-12	13-18
34. Mother										
35. Father										
36. Others										

37.A **In the past 6 months, have you regularly been exposed to cigarette, pipe, or cigar smoke during social or recreational activities?**
___Yes ___No

IF YES

37.B On average, how many hours per week have you been exposed to smoke?

_____Hours per week

Survey 1997 ID # 3/ ___

SCHOOLS ATTENDED OUTSIDE YOUR HOME COMMUNITY

38. Prior to coming to Yale, did you ever attend school in a location that was more than 25 miles away from your home community?

___Yes ___No

IF YES

Complete the following table.

List the locations where you attended school more than 25 miles away from your home community. Do not include Yale. Circle the type of school in each case.

TOWN/CITY	STATE	DATES OF ATTENDANCE
A. _____ Circle one: High Middle Elementary Pre.		From ___/___ mo yr To ___/___ mo yr
B. _____ Circle one: High Middle Elementary Pre.		From ___/___ mo yr To ___/___ mo yr
C. _____ Circle one: High Middle Elementary Pre.		From ___/___ mo yr To ___/___ mo yr
D. _____ Circle one: High Middle Elementary Pre.		From ___/___ mo yr To ___/___ mo yr

Survey 1997 ID # 3/ ___

OUTDOOR PHYSICAL ACTIVITY HISTORY

The following block refers to your typical outdoor physical activities during the 9 month academic year (i.e., September through May) in the years prior to coming to Yale.

			Before Age 6	Elem. School	Middle School	High School
39.	On average, how many days each week did you participate in outdoor physical activities?	Never				
		1-2 days/ week				
		3-4 days/week				
		Most days				
		Don't remember				
40.	How would you describe the outdoor activities noted above in terms of physical exertion? (check all that apply). See examples listed below.	Light				
		Moderate				
		Strenuous				
		Don't remember				
		Does not apply				

You may use the following list as a guide for answering questions 40 and 43.

Light Activities
sitting, leisurely walking, driving/commuting

Moderate Activities
baseball, volleyball, golf (carrying clubs),brisk walking bicycling leisurely, hiking

Strenuous Activities
jogging, tennis, badminton, fast bicycling, swimming, basketball, football, soccer, rollerblade, skating, acrobics

The following block refers to your typical outdoor physical activities during the 3 summer months (i.e., June through August)

			Before Age 6	Elem. School	Middle School	High School
41.	On average, how many days each week did you participate in outdoor physical activities?	Never				
		1-2 days/ week				
		3-4 days/week				
		Most days				
		Don't remember				
42.	On a typical outdoor activity day, how many hours did you spend doing these activities?	1 or less hours				
		2-4 hours				
		5-8 hours				
		More than 8 hrs				
		Don't remember				
		Does not apply				
43.	How would you describe the outdoor activities noted above in terms of physical exertion? (check all that apply). See examples listed above.	Light				
		Moderate				
		Strenuous				
		Don't remember				
		Does not apply				

Survey 1997 ID # 3/ ___

MISCELLANEOUS INFORMATION

44. Sex: ___Male ___Female

45. What ethnic /racial group would you consider yourself to be?

___White, not of Hispanic origin
___Black, not of Hispanic origin
___Hispanic
___Asian
___Native American
___Other _____ (Please specify)

46. What is the highest level of education achieved by your father:

___Did not Graduate from High School
___High School Graduate
___Technical/Trade School
___Some College
___College Graduate
___Graduate/Professional School
___Don't know

47. What is the highest level of education achieved by your mother:

___Did not Graduate from High School
___High School Graduate
___Technical/Trade School
___Some College
___College Graduate
___Graduate/Professional School
___Don't know

Thank you for your participation in this part of our study. If you have any remarks or suggestions about this questionnaire, please comment below.

ABOUT THE AUTHORS

Patrick L. Kinney received his doctorate in environmental science and physiology at the Harvard School of Public Health in 1986. His thesis work involved analysis of data from the Harvard Six Cities Study addressing the acute pulmonary effects of ozone. Dr. Kinney initiated the work described in this report at New York University's Institute of Environmental Medicine. There, and more recently at the Columbia School of Public Health, he has carried out epidemiologic studies addressing the human health effects of air pollution.

Maneesha Aggarwal received a master's degree in environmental sciences and a Ph.D. in air pollution from Jawaharlal Nehru University, New Delhi, India. She is currently working as a Post Doctoral Research Scientist at the Division of Environmental Health Science, Columbia University. Her interests are in air pollution modeling, exposure analysis, and air pollution epidemiology.

Sergey V. Nikiforov received his master's degree in chemical physics from Moscow State University. He is currently a doctoral candidate in Environmental Health Sciences at the Columbia School of Public Health.

Arthur Nadas received his Ph.D. in mathematical statistics at Columbia University. For many years, he worked in statistical software development at IBM Corporation, including work on speech pattern recognition. Dr. Nadas currently works in biostatistics on the faculty at the New York University Institute of Environmental Medicine.

PUBLICATIONS RESULTING FROM THIS RESEARCH

Nikiforov SV, Aggarwal M, Nadas A, Kinney PL. 1998. Methods for spatial interpolation of ozone concentrations. J Expos Anal Environ Epidemiol (in press).

ABBREVIATIONS

AIRS	Aerometric Information and Retrieval System
$FEF_{25\%-75\%}$	forced expiratory flow between 25% and 75% of forced vital capacity
HC	hydrocarbon
IQD	interquartile distance
LOESS	locally weighted smoothing scatterplots (regression)
MAX1	daily one-hour maximum ozone concentration
MAX8	daily eight-hour maximum ozone concentration
MID8	average ozone concentration between 10 a.m. and 6 p.m.
MID12	average ozone concentration between 10 a.m. and 10 p.m.
NO_x	oxides of nitrogen
ppb	parts per billion
$PM_{2.5}$	particulate matter less than 2.5 μm in diameter
PM_{10}	particulate matter less than 10 μm in diameter
R^2	multiple correlation coefficient squared
SD	standard deviation
SUM06	sum of all hourly ozone concentrations greater than 60 ppb

COMMENTARY
Health Review Committee

HEI

INTRODUCTION

Ozone, an oxidant gas, is a major component of air pollution. Because ozone causes adverse effects on the respiratory system, the U.S. Environmental Protection Agency (EPA)* established a National Ambient Air Quality Standard (NAAQS) for ozone that, until recently, was 0.12 parts per million (ppm), a level not to be exceeded for more than one hour once per year (Federal Register 1971). On the basis of recent scientific evidence that multihour exposure to lower levels of ozone may be harmful (reviewed in U.S. Environmental Protection Agency 1996a), the EPA changed the level and the form of the standard to 0.08 ppm measured over 8 hours, with four exceedances in three years allowed before an area is deemed out of compliance (Federal Register 1997).

Although there is an extensive literature on the effects of short-term exposure to ozone on the respiratory system, information on the health effects of long-term exposure is limited. Some animal studies and epidemiologic studies (discussed in more detail in the Scientific Background section, below) suggest that prolonged or repeated exposures to ozone may have deleterious effects. Studies addressing this issue, however, are technically challenging for several reasons. First, a nationwide system for measuring ambient ozone concentrations has been in existence only since 1975; second, actual personal exposures to ozone may differ substantially from ambient levels, leading to potential bias due to measurement error; third, both error and time variability affect measures of pulmonary function, especially of the small airways, which are thought to be primary ozone targets; and finally, exposure to other pollutants, including cigarette smoke, may confound ozone effects. Therefore, the development of improved methods to estimate human lifetime exposure to ozone and the impact of such exposures on health outcomes is critical.

In 1991, the Health Effects Institute organized the Environmental Epidemiology Planning Project to identify gaps in knowledge of the health effects of air pollutants such as ozone. Leading scientists identified several areas for further study, such as the development of accurate tools for assessing prolonged exposure to ozone in retrospective studies, including physiologic and biological markers to estimate the effects of such exposure (Health Effects Institute 1994). To complement the work of the Environmental Epidemiology Planning Project, HEI issued Request for Applications (RFA) 91-1, "Epidemiologic Studies of the Health Effects of Long-Term Ozone Exposure." A major goal of this RFA was to support the development of both methods for ozone exposure assessment and functional markers to measure its long-term effects.

The independent applications from Drs. Tager and Kinney and their associates were two of the six studies funded under RFA 91-1 by the HEI.[†] HEI funded both investigators to develop and refine methods for retrospectively estimating exposure to ozone. The objective of Dr. Tager's study, "Feasibility Study for Chronic Ozone Respiratory Effects," was to develop a new method for estimating a person's lifetime exposure to ozone and to construct a model of personal ozone exposure. As part of their research plan, Tager and colleagues also wanted to identify a reliable test of pulmonary function, especially small airway function, with a reasonable level of precision across a wide range of subjects. The investigators planned to apply this pulmonary function testing at a later date in large-scale epidemiologic studies of ozone effects. In their application, "Retrospective Characterization of Ozone Exposure," Dr. Kinney and colleagues proposed to evaluate whether the data from existing U.S. monitoring stations could be used to assess lifetime exposure to ozone. In addition, Dr. Kinney proposed to develop and test a questionnaire about the subjects' physical activity patterns at different stages of their lives.

Because of the similar objectives of these two studies, HEI encouraged Dr. Tager and Dr. Kinney to communicate with each other during the course of their studies. The common goals and approaches taken by Drs. Tager and Kinney also provided the HEI Review Committee with the opportunity to evaluate and compare the interpretations

*A list of abbreviations appears at the end of each Investigators' Report for your reference.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

[†] Dr. Tager's study was funded with a budget of $199,441 and began in September 1993. Dr. Tager submitted his Final Report in two parts: "A Study of the Variability of Volumes and Flows from Maximum Expiratory Flow-Volume Curves and the Slope of Phase III from the Single Breath Nitrogen Washout Curve," and "A Pilot Study to Assess the Reliability of Estimates of Lifetime Exposure to Ambient Ozone Derived from Questionnaires and Ambient Monitoring Data," which were received at HEI on September 19, 1995, and November 15, 1995, respectively. Revised reports were accepted on October 30, 1996. Dr. Kinney's study was funded with a budget of $230,646. The study began in November 1993 and was completed in October 1995. Dr. Kinney submitted a draft report for review in October 1996. A revised report was accepted on June 30, 1997.

and conclusions of the two studies in a single Commentary. During review of the two studies, the HEI Review Committee and the investigators exchanged comments and clarified issues in the Investigators' Reports and in the HEI Review Committee's Commentary. This Commentary is intended to aid HEI sponsors and the public by highlighting the strengths of these studies, pointing out alternative interpretations, and placing the reports into scientific perspective.

SCIENTIFIC BACKGROUND

A broad range of studies in both animals and humans suggest that exposure to ozone can lead to changes in function and physiology in all parts of the airways (reviewed in U.S. Environmental Protection Agency 1996b). These studies indicate that the effects of ozone are dependent not only on concentration, but also on the duration and pattern of exposure. Because ozone is primarily an outdoor pollutant with characteristic seasonal and daily peak levels, people who spend substantial time outdoors in vigorous activity, such as children playing and adults working or exercising, are particularly susceptible to its effects. The increases in breathing frequency and volume of air taken in during exertion are thought to heighten the doses of ozone that reach the airways.

Short-term exposure to ozone is frequently associated with reversible clinical symptoms such as cough, shortness of breath, and bronchoconstriction (reviewed in U.S. Environmental Protection Agency 1996b). Elevated ambient levels of ozone have also been associated with increased emergency department visits and hospital admissions for respiratory problems (U.S. Environmental Protection Agency 1996b), and in some studies, with increased mortality (Kinney and Özkaynak 1991). However, because ambient ozone levels rise and fall in partial correlation with other pollutants, it is not clear whether the association between the latter health outcomes and ozone is one of cause and effect.

In some people, inhaled ozone alters measures of pulmonary function, including a decrease in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Decrements in FEV_1 are believed to reflect ozone-induced changes in the function of both the large and small airways (Gong et al. 1986; Hazucha 1987; Folinsbee et al. 1988; U.S. Environmental Protection Agency 1996b). Within the lungs of animals exposed to ozone, the primary sites of tissue damage are the small airways, specifically the terminal bronchioles and the gas-exchanging centriacinar region. Models also predict that in humans these areas of the small airways are subject to the highest levels of ozone (Boorman et al. 1980; Fujinaka et al. 1985; Miller et al. 1985; Overton and Graham 1989). In addition, some studies have shown decreases in measures of small airway function, such as forced midexpiratory flow ($FEF_{25\%-75\%}$, a measure of airflow), following acute exposure of humans to ozone (Keefe et al. 1991; Weinmann et al. 1995). In clinical studies, many individuals who are exposed to ozone for periods up to a few hours exhibit a rapidly induced inflammatory response in the airways (as evidenced by the appearance of markers of inflammation in the bronchiolar lavage fluid), which resolves after approximately 24 hours if the exposure is not repeated (U.S. Environmental Protection Agency 1996b). Inflammation does not appear to correlate with ozone-induced changes in FEV_1 and FVC (Koren et al. 1989; Balmes et al. 1996, 1997; Frampton et al. 1997; Torres et al. 1997).

Most of the field studies and controlled chamber studies on ozone pollution provide information on acute respiratory effects. Such studies do not, however, provide information about the consequences of prolonged exposure, nor do they address whether ozone exposure causes or exacerbates lung diseases such as pulmonary fibrosis, emphysema, asthma, or chronic bronchitis. Most of the information on long-term effects of ozone exposure comes from animal studies in which investigators can control experimental variables. For example, prolonged exposure to ozone causes mild to moderate structural changes and an increase in collagen in the centriacinar region of the lung of healthy rats (Chang et al. 1992, 1995; Last et al. 1994; Catalano et al. 1995; Pinkerton et al. 1995). In rats, these changes appear to have had little or no measurable impact on pulmonary function, with the exception of a small decrease in residual volume (Harkema and Mauderly 1994; Catalano et al. 1995; Costa et al. 1995).

The physiologic or clinical consequences of long-term exposure to low or moderate levels of ozone have been addressed in a limited number of epidemiologic studies. These studies have been difficult to evaluate for several reasons: (1) problems with estimating personal exposure over many years; (2) the use in population studies of spirometric tests of respiratory function, which are relatively straightforward but may not be sensitive indicators of ozone effects; (3) high within- and between-individual variability in tests of small airway function, which may be more sensitive to ozone; (4) difficulty in controlling for confounding factors, such as ambient particulate matter, that may correlate with ozone levels.

A study of Seventh Day Adventists who had lived in the same region of California for more than 10 years (the Adventist Health Smog Study), one of the most comprehensive of these epidemiologic studies, examined the effects of pollutants on a number of clinical endpoints (Abbey et al.

1991a). The estimate of personal exposure to ozone was based on interpolations from existing ozone monitoring sites, with adjustments for time the subject spent indoors and outdoors (Abbey et al. 1991b). However, the investigators did not test the subjects' pulmonary function. The study showed a weak association between ozone exposure and the incidence and severity of asthma, but this association was reduced to insignificant levels when measures of particulate matter were included in the model. The investigators found no association between ozone exposure and respiratory symptoms. In a later study, these investigators found that ozone was associated with a slightly increased risk of asthma (Abbey et al. 1993). Again, however, it was not clear whether this result was due to ozone alone, because of the difficulties in partitioning the effects of ozone vis-à-vis particulate matter.

In a prospective cohort study, Detels and associates (1987) examined lung function in residents of two California communities with different levels of ozone. The investigators did not attempt to estimate personal exposure, but assigned study subjects to "high" or "low" ozone exposure categories. Detels and associates found that subjects who had been most heavily exposed to oxidant pollution had decreased FEV_1 and ΔN_2 (a parameter of small airway function) at the beginning of the study and an accelerated decline of lung function over time. The impact of this study was limited, however, by loss to follow-up, as only approximately 50% of the original subjects were retested. In addition, the investigators could not control adequately for other pollutant differences between the communities. In a later study comparing two different California communities with differing combinations of ozone and other pollutants, ΔN_2 and most spirometric measures were significantly worse in the subjects from the high-pollution community (Detels et al. 1991). However, extensive loss to follow-up, imprecise ozone exposure characterization, and methodologic differences in measuring lung function parameters in the two communities have added to the difficulty of interpreting these data.

Other investigators have suggested that prolonged exposure to high levels of ozone decreases some parameters of lung function and may affect clinical endpoints (for example, see Schmitzberger et al. 1993; Stern et al. 1994), but these epidemiologic studies suffer from many of the problems of those previously described, particularly the inability to distinguish the effects of ozone from other pollutants, and the difficulty in assessing individual exposure. Thus, taken together, these epidemiologic studies suggest that long-term human exposure to ozone may cause chronic changes in airway physiology and function, but do not provide definitive results.

Critical issues remain in determining the long-term effects of ozone exposure in humans. Because of the reported variability in measures of small airway function, both from person to person and from test to test (for example, see Cochrane et al. 1977; Vollmer et al. 1990), finding a reliable test for measuring the effects of ozone on small airway function is highly desirable. In addition, accurate estimation of individual levels of exposure—past and present—is crucial. A network of ozone monitoring sites is in place across the United States, but it is not clear how the information from fixed outdoor monitoring sites can best be used to estimate personal exposure, or what level of accuracy can be attained; for example, the level of ozone may vary with distance from its source, the ozone level measured at a monitoring site may not reflect ambient exposures away from the monitoring site, and people may spend most of their time indoors. Exposure to ozone is generally lower indoors than outdoors, but individual exposure is also modified by the type of residence. Indoor exposure can be significant, as a consequence of using appliances such as electronic air cleaners, the longer times that most individuals spend indoors, and air exchange between outdoors and indoors (Contant et al. 1987; Hayes 1991; Wechsler et al. 1989). Finally, individuals' activity patterns, particularly during their time outdoors, will modify their exposure to ozone.

HEI funded the investigations by Drs. Tager and Kinney to address these issues. To improve estimates of individual exposure to ozone, Tager and Kinney developed new approaches for retrospectively estimating cumulative ozone exposure. Both investigators developed and administered a questionnaire to young adults attending college, focusing on factors they deemed crucial in determining individual ozone exposure patterns. In addition, Kinney assessed the accuracy with which different types of models determined exposure to ozone at a given point. Tager also investigated tests of lung function to determine which would be the most appropriate ones to use in larger studies. These studies are discussed in detail in the subsequent sections. Key features of the two studies are illustrated in Table 1.

TECHNICAL EVALUATION OF DR. TAGER'S REPORTS

OBJECTIVES

Dr. Tager's overall objective was to develop methods to be used in future epidemiologic studies to determine the relation between long-term exposure to ambient ozone and alterations in measures of small airway function. Studying students attending the University of California at Berkeley (UCB) offered an opportunity to evaluate adolescents and

young adults who could provide data relevant to the estimation of ozone exposure over their lifetimes. In addition, this population provided an opportunity to study young adults who had lived their entire lives in either of two regions with different levels of air pollutants: the Los Angeles Basin or the San Francisco Bay Area. The eligibility criteria for inclusion in the study were (1) age 16 to 20 years, (2) being a lifelong nonsmoker, (3) having no history of asthma (modified to no treatment or symptoms of asthma in the teen years), and (4) lifelong residence in the Los Angeles Basin or San Francisco Bay Area.

Tager and coworkers divided their study into two parts. In Part I, to identify the most reliable test of small airway physiology, they administered lung function tests to a group of UCB students on two different occasions. They determined the variability of results between test sessions 1 and 2 for any one individual (within-subject variability), and the variability between subjects on any given test (between-subject variability). In Part II, the investigators developed a questionnaire to use in conjunction with historical ozone measurements at ambient monitoring sites to make retrospective assessments of individual ozone exposure. Although not part of their original aims, the investigators also conducted a preliminary investigation to evaluate lung function in students who had grown up in either high- or low-ozone environments.

PART I. PULMONARY FUNCTION TESTS

Study Design

As described above, some but not all epidemiologic studies have reported that certain measures of small airway function are affected by long-term ozone exposure. These tests of small airway function, however, have high within- and between-individual variability. Tager and colleagues evaluated two methods for assessing pulmonary function: maximal expiratory flow-volume (MEFV) curves (using American Thoracic Society [1991] standardized methods), and the single-breath nitrogen washout (SBNW) test (using protocols based on National Institutes of Health standard methods). As part of their protocol, the investigators measured five different parameters of pulmonary function, de-

Table 1. The Approaches Used by Tager and Kinney to Estimate Personal Lifetime Exposure to Ozone

	Tager	Kinney
1. Key factors used to estimate personal exposure	a. Questionnaire about residence, time spent outdoors, and level of activity (based on long-term residence) b. Ozone estimate based on ambient monitoring data	a. Questionnaire about residence, time spent outdoors, and level of activity (based on life epoch) b. Ozone estimate based on ambient monitoring data
2. Study subjects (and number in study)	UC Berkeley students, aged 17–21 years (Part I: 239; Part II: 175 for questionnaire reliability, 130 for lung function)	Yale University students, aged 17–21 years (52 for questionnaire reliability; 200 for long-term ozone estimates)
3. Residence requirements for study subjects	Lifetime residence in either Los Angeles Basin or San Francisco Bay Area	No more than one year outside the U.S.
4. Origin of ambient ozone data	California sites: California Air Resources Board	National network: EPA Aerometric Information Retrieval System
5. Method for estimating ozone exposure at residence	Inverse-distance squared, based primarily on data from one or three nearest sites	Evaluated different models, including inverse-distance squared, regression, and kriging
6. Evaluated contribution of time spent indoors?	Yes, time spent indoors "weighted" at 0.2 or 0.5	No
7. Questionnaire assessment	Test/retest 5–7 days apart	Test/retest 1 month apart

fined in the accompanying sidebar. Four of these parameters, FVC, FEV_1, $FEF_{25\%-75\%}$, and $FEF_{75\%}$, were derived from the MEFV curve; and a fifth, ΔN_2, from the SBNW test (see sidebar). To determine within-subject and between-subject variability for each parameter of lung function, the tests were administered twice to 239 subjects, five to seven days apart.

Results and Interpretation

The key findings of Part I of Tager's study are as follows:

- There was a hierarchy of within-subject variability, expressed as a coefficient of variation (CV), for the different parameters of lung function, within a single test session and from session to session.
- Measurements often considered to reflect large airway function, FEV_1 and FVC, had the lowest CV, that is, were the most reproducible.[‡] For measurements considered to reflect small airway function, $FEF_{25\%-75\%}$ and $FEF_{75\%}$, CVs were somewhat higher, but still in an acceptable range. In contrast, the CV for ΔN_2, also thought to reflect small airway function, was considerably higher than those for $FEF_{25\%-75\%}$ or $FEF_{75\%}$.
- Acute respiratory conditions such as colds and flu and more chronic conditions such as asthma had little effect on the variability of the pulmonary function parameters measured.

The investigators concluded that measuring either $FEF_{75\%}$ or $FEF_{25\%-75\%}$ would be suitable for future epidemiologic studies of ozone effects on small airway function, but measuring ΔN_2 would not.

Part I of the study was carefully performed with the worthwhile goal of assessing within- and between-subject variability of measures of small airway function, the airways considered to be most sensitive to the long-term effects of ozone. For more than 20 years, there has been great interest in finding lung function tests that are sensitive enough to measure pathophysiologic changes in the small airways (discussed by Wright et al. 1992; Scanlon and Hankinson 1996). In the early 1970s, attention focused on the SBNW test in the belief that identifying smokers with early pathophysiologic changes in the small airways would be a way to identify the subset of smokers who were at greatest risk of progressing to clinically significant airway obstruction. Many studies demonstrated that the SBNW test was more sensitive than the MEFV curve, but the value of the SBNW test was limited by large within- and between-individual variability (for example, see Hayes and Christiani 1993). These findings have been corroborated by Tager's study: his efforts at quality control were unable to reduce the CV of ΔN_2 derived from the SBNW test. This was perhaps not surprising given the study population, which was young and nonsmoking, that is, with small ΔN_2 values.

[‡] We use "accuracy" (synonymous with "validity") to refer to how close an observation is to the quantity it is intended to measure. We use "precision" to refer to the statistical dispersion of measurements among themselves, without regard to consistent errors (synonyms: reliability, reproducibility, consistency).

PART II. ESTIMATING LIFETIME OZONE EXPOSURE

Study Design

In Part II of their study, Tager and colleagues designed an approach for retrospectively estimating individual lifetime exposures to ozone, based on a questionnaire designed to track an individual's residences and activity patterns combined with historical ozone monitoring data. The questionnaire requested information about residential history since birth, including street addresses, ZIP codes, and dates of residence. It also asked about time spent in and level of outdoor activities and about home ventilation patterns, particularly as they related to the months May through October when ozone levels are highest in the Los Angeles Basin and the San Francisco Bay Area and when young people may spend more time outdoors. To determine the precision of questionnaire responses, Tager and colleagues readministered the questionnaire to the study population five to seven days after the initial test.

The investigators used data from the California Air Resources Board to derive monthly averages of ozone levels in designated ZIP code areas between 1975 and 1992, giving special attention to two monthly averages: 10 a.m. to 6 p.m.

MEASURES OF PULMONARY FUNCTION

FVC (forced vital capacity) — the total volume of air expelled from the lungs following maximal inspiration.

FEV_1 (forced expiratory volume in one second) — the volume exhaled during the first second of a forced expiration following maximal inspiration.

$FEF_{25\%-75\%}$ (forced midexpiratory flow) — the mean rate of airflow between the volumes representing 25% and 75% of the FVC.

$FEF_{75\%}$ — the instantaneous flow at the point representing 75% of the FVC.

ΔN_2 — the slope of phase III of the single-breath nitrogen washout (SBNW) curve.

average ozone (the hours of highest ozone level and referred to as MID8 in the accompanying study by Kinney et al.), and average hours per month with an ozone concentration greater than 60 ppb (SUM06 in Kinney et al.). These averages were selected because there were clear differences in distribution between the Los Angeles Basin and San Francisco Bay Area and there was a reasonable distribution of values within each of the regions.

To estimate ozone exposure for an individual living in a specific ZIP code area, monitoring data were spatially interpolated using an inverse-distance-squared weighting. Generally, the interpolation was based on data from the three nearest monitoring stations, but if a measurement was available from a station within 5 miles of the center of the ZIP code, this value alone was used (more than 50% of the subjects fell into this latter category). For the purpose of this analysis, Tager assumed that outdoor ozone exposure was five times higher than indoor exposure. The investigators tested different models to see how the estimates of ozone exposure varied with the assumed time spent in different ozone environments and with level-of-activity data.

Results and Interpretation

The key findings of Part II of Tager's study are as follows:

- The questionnaire test/retest precision for residential history was high, particularly if the subjects had lived in only one or two residences over their lifetimes. Precision decreased when subjects had lived in more residences for shorter times.
- As expected, the investigators found that UCB students who had resided for a long time in the Los Angeles Basin had higher estimated ozone exposures than students who had lived in the San Francisco Bay Area.

This study shows that it may be possible to construct a useful profile of personal ozone exposure by combining questionnaire information about area of residence, type of residence, and level of outdoor activity with data from local ozone monitoring stations. However, several concerns need to be addressed before Tager's technique will be fully ready for use in a large-scale epidemiologic study. The major issue is that the investigators made assumptions that seem theoretically reasonable, but have yet to be tested empirically. Testing these assumptions was not part of their study design.

One such assumption was that ozone levels do not vary over a ZIP code area, the basic geographic unit they used to estimate outdoor exposure. However, because the geographic scale on which ozone varies is not known accurately, it is possible that ambient levels of ozone vary substantially within a ZIP code area. The investigators also assumed that interpolated estimates of outdoor ozone levels based on data obtained from the single nearest monitoring site would be sufficiently accurate, because a high percentage of their study subjects lived within 5 miles of a California monitoring site and single monitoring site data were only used in instances when the distance from the monitor to the residence was 5 miles or less. In Kinney's accompanying nationwide study, estimates based on the three nearest sites were significantly more accurate than those based on only the single nearest site. (In Kinney's study, however, distances from monitoring sites were generally larger than 5 miles, so it is difficult to compare directly the findings presented in the different reports.) Kinney also showed that his estimates of ozone exposure were least accurate in California, perhaps because high local variations make estimates less accurate on a relative as well as on an absolute scale.

To estimate personal exposure, Tager and associates "weighted" the subjects' indoor exposure to ozone (I) at either 0.2 or 0.5 the level outdoors (O); that is, they set I/O ratios at 0.2 and 0.5. Several studies have shown that I/O ratios are quite variable for buildings with different ventilation rates; for example, in Yocum (1982), they varied from 0.1 to 0.7; in Druzik and associates (1989), from 0.24 to 0.75; and in Wechsler and associates (1989), from 0.24 to 0.71.

Although Tager found the precision of answers to his questionnaire to be high on retest, the second test was administered only five to seven days after the first. Readministering the questionnaire after a five- to seven-day interval may test the precision of the subject's recent memory more than the accuracy of the residence and activity information. Accuracy may have been tested more effectively by sending selected sections of the questionnaire, particularly on outdoor activity, to the parents of participants, as the investigators had originally proposed. Kinney, who used a similar questionnaire, found precision only moderate when the questionnaire was readministered after one month. Furthermore, subjects with different backgrounds and with less experience in answering questionnaires may not show the same level of test/retest precision as college students.

Finally, as discussed in the following section, the results of a pilot study showed decreases in some measures of small airway function in subjects who had high estimated lifetime exposures to ozone. However, these differences among UCB students who grew up in different ozone environments cannot be considered a validation of Tager's model of ozone exposure estimation. A more appropriate test of the accuracy of the investigators' model would be to compare estimates of ozone exposure with actual measurements of ozone levels, for example, by standard ozone monitors, rather than with health outcomes.

Preliminary Study of Lung Function and Estimated Ozone Exposure

Tager and colleagues examined lung function in 130 of the 175 subjects from Part I of their study whose past exposures to ozone had been estimated from questionnaire responses. The students with the highest estimates of cumulative ozone exposure had lower values of $FEF_{75\%}$ and $FEF_{25\%-75\%}$ than those who had the lowest estimates of cumulative exposure. The investigators found an inconsistent relation between the estimates of lifetime exposure to ozone and the measures of lung function FVC and FEV_1, which are believed to represent central airway physiology. Furthermore, the investigators did not find a correlation between ozone exposure and the measure ΔN_2, contrasting the findings of Detels and associates (1987).

Tager and coworkers concluded that long-term exposure to ozone appeared to be related to specific alterations in the function of small airways (measured by $FEF_{75\%}$ and $FEF_{25\%-75\%}$), rather than the function of central airways (measured by FVC and FEV_1). They noted that these findings are consistent with the predicted site of maximum effect of ozone, namely, the small airways of the human lung, and especially the centriacinar region.

This conclusion is important and provocative, but should be considered preliminary. Tager and colleagues did fit their model with ethnicity as a covariate, but the data were not sufficient to determine whether the inclusion of ethnicity improved the model significantly. In addition, because ozone exposures in the two areas of study showed almost no overlap, it is possible that some other, unknown factor that differed between the regions may have contributed to the findings. More careful exploration of these issues is required. Future studies involving larger populations, more carefully matched for ethnicity, using validated estimates of ozone exposure, and controlling for indoor air contaminants (for example, passive smoke) may help to resolve these problems of interpretation.

The biological and clinical significance of small decreases in airway function, such as those described by Tager and colleagues, has been highly controversial for many years. It has not been established that the modest changes in small airway function described by Tager and associates are predictive of future disease or loss of function (discussed by Wright et al. 1992; Scanlon and Hankinson 1996). Many different insults, such as tobacco smoking (to which the investigators refer), passive smoke, and a variety of air pollutants, may lead to minor abnormalities in the results of small airway function tests. Thus, not only is it difficult to ascribe a small change in airway function to a particular agent, but also the clinical significance of a small change in $FEF_{75\%}$ or $FEF_{25\%-75\%}$ is not well understood.

CONCLUSIONS

First, the finding that the measures of lung airflow $FEF_{25\%-75\%}$ and $FEF_{75\%}$ are reproducible from test to test and have an acceptable range of variability from person to person, consistent with the findings of previous investigators, suggests that these measures can be used in future large-scale epidemiologic studies to measure relatively subtle changes in small airway function.

Second, the finding that questionnaire data about residence and lifetime activity patterns can be combined with estimates of personal exposure derived from ambient ozone monitoring data implies that the profile of an individual's lifetime exposure to ozone can be obtained. As indicated in the previous sections, however, the investigators did not test the accuracy of their modeled estimates, so it is not clear how close these (reproducible) estimates are to true, personal ozone exposure levels.

Third, the preliminary finding that the highest estimated lifetime exposures to ozone were associated with lower $FEF_{25\%-75\%}$ and $FEF_{75\%}$ suggests an association between prolonged human exposure to ozone and adverse effects on small airway function. Although this finding is far from certain, it is consistent with the observation that ozone effects are first detected in the centriacinar region of the lung. Because of the limitations described above in modeling ozone exposure, as well as in the makeup of the groups in the current study, this finding should be considered preliminary, pending further and independent substantiation.

TECHNICAL EVALUATION OF DR. KINNEY'S REPORT

OBJECTIVES AND STUDY DESIGN

The overall goal of the study by Dr. Kinney and his colleagues was to develop methods for estimating retrospective exposures to ozone. His specific aims and study design were as follows:

- **To evaluate different methods (statistical models) for estimating ozone levels.** Kinney computed a 10-year summer average ozone level for each station in the nationwide ozone monitoring network. He then evaluated different models to determine whether he could predict the ozone level at a particular site from measurements reported at nearby stations. Kinney then determined the accuracy of the prediction by comparison with the actual measurement at the site.
- **To develop and test a questionnaire for assessing lifetime ozone exposure.** Kinney developed and tested a questionnaire, which he administered to students at

Yale University who had previously lived in different regions of the United States. Kinney's approach resembled Tager's in its focus on residence information and level of individual activity; however, Kinney concentrated on specific life epochs described by school level, whereas Tager asked questions about long-term residence. Kinney evaluated the precision of the questionnaire by retesting one month later.

- **To estimate long-term ozone exposure in a group of students and the variability of ozone levels over time and space, and to design a retrospective cohort study of the effects of long-term ozone exposure on young adults.** Kinney estimated exposure to ozone over a 10-year period for each of 200 Yale University students who had completed his questionnaire, using the model that seemed to provide the most accurate estimates. From this he estimated a mean ozone exposure for the group over 10 years, plus the associated variance and standard error terms. To derive estimates of temporal and spatial variability in ozone levels, he divided the variance term into within-subject and between-subject components, respectively. To estimate the minimum number of subjects needed for a future epidemiologic study to be reasonably sure of showing ozone-related differences in lung function, he combined the between-subject variance he had derived with the ozone-induced change in lung function found by Tager in the accompanying study.

METHODS FOR ESTIMATING OZONE EXPOSURE

The investigators obtained hourly ozone measurements from all U.S. monitoring sites for which data were available between 1981 and 1990 (between 605 and 702 sites in any one year), using the Aerometric Information and Retrieval System (AIRS). Because the measure of ozone that best relates to health effects is not known, the investigators computed five different ozone metrics: the daily one-hour maximum (MAX1), by which the ozone NAAQS had previously been defined; the daily maximum 8-hour running average (MAX8), which the EPA has proposed as the new ozone metric; the average concentration between 10 a.m. and 6 p.m. (MID8), the hours of the day when people are most active; the average concentration between 10 a.m. and 10 p.m. (MID12); and the sum of all hourly concentrations greater than or equal to 60 ppb (SUM06). The investigators then computed daily and monthly means for each measure. As expected, they found that the highest measures of ozone were recorded in the summer months, June, July, and August. When MAX1 was calculated for each year, they also found that nationwide, average ozone levels did not vary significantly from year to year between 1981 and 1990. To facilitate comparisons of different methods of estimating ozone levels, the investigators derived a single number, the average for the summer months over the 10 years studied, for each metric at every monitoring site.

The investigators estimated ozone concentrations at a particular site by four different methods: (1) the simple average of k nearby sites, where k is the number of monitoring sites closest to the site being monitored; (2) the inverse-distance-weighted average of k nearest sites; (3) the inverse-distance-squared-weighted average of k nearest sites; and (4) regression on k nearest sites. The investigators used these interpolation methods in turn to estimate average summer ozone concentrations at each U.S. monitoring site based on the data from up to 10 nearest sites. This calculation was repeated for each of the five ozone metrics. An additional method, known as "kriging", was used to derive estimates for two subsets of sites: those in California and those in the New York/New Jersey/Connecticut (NY/NJ/CT) tristate region.

To assess the precision of the estimation, the investigators calculated the SD of the difference between the ozone concentration measured at the site and the value estimated by the prediction. The size of the SD was referred to as the interpolation error; the smaller the SD or interpolation error, the closer the fit to the observed value.

Key Findings

The key findings of this part of Kinney's study were as follows:

1. All models tested gave similar results, but the regression-based model gave estimates with slightly smaller errors than the other models. Using the regression model, the investigators found that the errors decreased when more than one site was used in the calculation, but this improvement in accuracy was marginal after the third site was added. For the other models tested, error was reduced with more nearby sites included but actually became worse as more distant sites were added.
2. Using the three-site regression-based model:
   - The inclusion of other factors—covariates—had little effect on the estimated error of estimates. The covariates evaluated were meteorologic variables (average summer season temperature, relative humidity, and wind speed from the three weather stations closest to the ozone site), population density, and site elevation.
   - Distance from a monitor did not affect the accuracy of the regression-based estimate. Interpolation errors slightly decreased when the nearest monitoring site was more than 30 miles away.

- The regions where the regression-based estimates differed most, in both absolute and relative terms, from actual readings were predominantly in California (mostly around Los Angeles) and the NY/NJ/CT tristate area.

3. Kriging, a distance-based model, gave slightly more accurate estimates than the three-site regression model for data from California and the NY/NJ/CT area.

Interpretation

Kinney and colleagues concluded that reasonably precise estimates of ozone can be obtained for the United States using a regression-based method. For example, they found the error of the three-site regression model to be only 13% of the mean for the ozone measure. Estimates in California and in the NY/NJ/CT metropolitan area were less accurate because these areas have the greatest relative variability in ozone concentrations in the United States. The finding that the three-site regression model accurately estimated ozone levels even when the nearest monitoring site was more than 30 miles away suggests that proximity to a monitoring site is not crucial to accurate estimation. As ozone monitoring sites that are far apart tend to be in rural areas, these results are reassuring in demonstrating that this approach to estimating ozone concentrations can be applied to most regions of the United States.

In a second approach to investigate the impact of distance on ozone estimates, the investigators also assessed a distance-based interpolation model, kriging. The first step in this two-stage analysis was to work out the variation in spatial pattern of the data at sampled sites (deriving a function referred to as the variogram). In the second stage, the variogram was used to develop a weighted moving-average estimate at unsampled locations; thus, in this analysis, values at nearer sites were given a higher weight. Because current kriging software cannot handle the nationwide data set, the investigators tested only subsets of their data from California and from the NY/NJ/CT tristate region. Kinney and colleagues found that kriging performed slightly better than the regression model for the California and NY/NJ/CT subsets of data, suggesting that distance-based models may be useful in making future estimates of ozone exposure. Because the kriging analysis incorporates data from more sites than the other models, which would also improve the accuracy of estimates, it will have to be tested on the complete U.S. data set before firm conclusions can be drawn about how distance from a monitoring site affects the errors in interpolation estimates.

DEVELOPING AND TESTING A QUESTIONNAIRE TO ASSESS ACTIVITY HISTORY

To improve personal estimates of exposure to ozone, Dr. Kinney and colleagues developed a self-administered questionnaire, which they gave to students at Yale University. It included questions about activity patterns at different stages of life. The investigators evaluated the test/retest precision of the section on lifetime activity by readministering the questionnaire after an interval of one month. The precision of the test was computed using simple and weighted kappa statistics, which measure how much repeated measurements agree beyond the agreement expected by chance alone.

The activity history section of the questionnaire showed only moderate precision on retest after one month. This finding implies that the answers given by subjects aged 17 to 21 years about their level of activity a few years earlier may not be sufficiently precise for epidemiologic studies. More information is needed to determine how precision can be improved before applying this type of questionnaire-based approach in future studies with broader populations. For example, other questions or alternative wording of the same questions may elicit more precise answers on retest. As with Tager's questionnaire, readministering the questionnaire after a short interval mixes *validation* of the information provided with a measure of the *reliability* of the subject's memory.

ESTIMATES OF LONG-TERM OZONE EXPOSURE, AND THE VARIABILITY OF OZONE LEVELS OVER TIME AND SPACE

Kinney estimated between-subject and within-subject variances of ozone exposure over 10 years for each of 200 Yale University students. He applied the three-site regression model to residential information from each student's questionnaire to estimate a mean ozone exposure over the 10 years plus variance terms for the entire set of students, including within- and between-subject components.

For his estimate of long-term ozone exposure, Kinney found that the within-subject variance was approximately 40% of the between-subject variance, and similar in magnitude to the error in estimating ozone concentration by the three-site regression method. Kinney assumed that within-subject variance corresponded to temporal variability in ozone, that is, the difference in ozone levels that one person would be exposed to at different times. However, the within-subject component also includes errors in residential history, errors in the monitoring data, and other sources of variation. He also assumed that the between-subject

variance corresponded to spatial variability in ozone levels, that is, the additional variation in exposure of different individuals who would experience greater differences in levels of ozone in different places. He concluded from his calculation that variation in estimates of long-term ozone exposure between subjects was almost 2.5 times greater than variation within a subject over time.

DESIGN OF FUTURE EPIDEMIOLOGIC STUDIES

Kinney estimated the minimum number of subjects that would have to be enrolled in a future epidemiologic study to demonstrate a physiologic effect of ozone on human lung function. He based his calculation on two inputs: (1) the between-subject variance for a population exposed to ozone, derived from his Yale student study; and (2) an assumed effect of ozone on a measure of small airway function, $FEF_{25\%-75\%}$, derived from Tager's accompanying pilot study of 130 UCB students (see Part II of this Research Report and Künzli et al. 1997). From this calculation, Kinney estimated that approximately 100 subjects would be needed for a future epidemiologic study to quantify long-term ozone effects.

As Kinney acknowledges, however, this calculation is based on a number of assumptions that may not hold. For example, the between-subject variance in Yale students may not be representative of the variance in exposure levels of individuals enrolled in a future study, and the size of the ozone effect on $FEF_{25\%-75\%}$ observed by Tager and colleagues (Part II of this Research Report, Künzli et al. 1997) may be greater or smaller in a future study. Furthermore, as neither Kinney nor Tager validated their exposure models, power estimates for a future epidemiologic study should be regarded as first approximations only.

CONCLUSIONS

The finding that reasonable estimates of past ozone levels can be derived from monitoring data using a regression-based model involving the three nearest sites suggests that this method may be useful in future epidemiologic studies. Interestingly, Kinney's finding that estimates were least accurate in California and the NY/NJ/CT metropolitan region emphasizes the difficulty of estimating ozone exposure in regions of highly variable ozone levels.

Although including covariates such as meteorologic variables and population density did not substantially improve the nationwide estimates, Kinney speculated that the inclusion of other covariates, such as the distribution of wind direction and wind speed, and the use of more complex models might improve the accuracy of the estimate. Future studies will determine whether such approaches can improve the accuracy of estimates.

Using a regression-based model, Kinney concluded that distance from the nearest monitors played little role in determining the accuracy of the estimate. This suggests that rather accurate regression-based estimates of ozone concentration can be made even in rural areas, indicating that the density of available monitoring sites appears to be adequate for estimating ambient ozone concentrations averaged over time and over distance, up to the distance between monitors. However, because the variability of ozone over small distances is not known, ozone measurements at the monitoring sites may not reliably estimate spatial variability within small subsections of the region. Interestingly, when Kinney tested a distance-based model, kriging, on the subset of data from California and the NY/NJ/CT region, this model gave somewhat more accurate estimates than the three-site regression-based approach. This finding suggests that distance from an ozone monitor may influence the accuracy of the estimate in some models. The role of distance in determining the accuracy of estimates will require further study.

DISCUSSION OF THE TAGER AND KINNEY STUDIES

The studies by Tager and Kinney and their associates are important efforts for developing methods for retrospectively estimating an individual's lifetime exposure to ozone. Both investigators used fixed-site ambient monitoring data accumulated over many years and devised models to estimate ozone concentrations at locations distant from the monitoring site. In order to obtain estimates of personal exposure, they assumed that ozone exposure would be highly influenced by both the time each person spent outdoors during periods of peak exposure and the individual's level of activity while outside. Tager and Kinney incorporated these variables into questionnaires that they developed to calculate individual exposure to ozone.

Two remaining issues should be addressed before these methods are applied in large epidemiologic studies. One issue is *validation*. Does the method really measure what it is supposed to measure (a matter of statistical bias)? The other is *reliability*. Do measures of the same exposure taken at different times or with different instruments give approximately the same answer (a matter of statistical variance)?

Though both Tager and Kinney conducted feasibility studies, validation was not the aim of either investigator. Looking ahead, a logical next step will be to validate the

results independently, using more closely matched groups. An ideal approach would be to compare the investigators' estimates with data from personal (passive) monitors worn by a small sample of individuals at a variety of places and times. However, this approach assumes that an accurate and precise passive monitor is available. As yet, however, the personal ozone monitors now available have not been validated in natural settings in which subjects move around freely (for example, see Liu et al. 1997). Another way to validate exposure estimates would be to conduct a series of smaller studies that use stationary monitors to assess ozone concentrations in various microenvironments and then combine these measured concentrations with time-activity patterns of individuals to estimate exposure. These approaches have the potential to provide a partial validation of the estimation procedure, but could not validate the data themselves in the absence of personal monitor information from each prior life epoch.

There is also a need for further assessment of the reliability of the information provided by answers to the test questions, particularly those dealing with individual times and levels of outdoor activity in the distant past. Using the results of Tager and Kinney to compare the reliability of student answers to questions about activity and residence is difficult because the investigators used different survey instruments. Nevertheless, some inferences can be made. Both studies approached this issue by readministering the questionnaire after an interval, and both assessed the reliability using weighted kappa statistics. Kinney found "fair to moderate" agreement of answers after a one-month gap, and Tager found "high" agreement after five to seven days. With such brief intervals between tests, however, it is difficult to judge how much of the observed reproducibility is a result of carryover effects of the first test. The current studies do not provide information about the sources of error in the calculations of precision, how the precision of answers could be improved, or whether the inclusion of other types of data would enhance the precision of the questionnaire. Thus, it is not clear whether Kinney's approach to estimating ozone exposure based on life epochs is more or less reliable than Tager's residence-based approach. Further work may show that each has a place in certain kinds of studies.

In the near future, the methods developed by Drs. Tager and Kinney will be of greatest value in epidemiologic studies involving young subjects. Though a national system for monitoring ozone levels has existed only since 1975, it covers almost the complete life span of the subjects in both the Tager and Kinney studies (age range 16–21 at the time of their studies). In contrast, this time span represents only a small fraction of the life of older subjects, creating uncertainty about making retrospective estimates for this age group. In addition, the precision of answers to questions concerning the amount and level of lifelong outdoor activity may be of greater concern for persons asked to recall events many decades earlier than for college students recalling a period less than 20 years previously.

In summary, there is a need to develop a means to produce precise, retrospective estimates of personal exposure to ozone (and other air pollutants) in order to assess the effects of such exposures on lung function. Of necessity, such estimates require a number of assumptions, many of which are difficult to verify, especially in the absence of a "gold standard" against which the estimates can be verified. Tager and Kinney have taken important steps in developing approaches for retrospective estimation of past exposures to ozone (and in Tager's case, for evaluating airway function in young subjects). The approaches are now ready to be pilot tested and, to the extent possible, validated. If such validation studies are successful, the investigators' methods should advance air pollution epidemiology.

ACKNOWLEDGMENTS

The Health Review Committee would like to thank the reviewers for their help in evaluating the scientific merit of the Investigators' Reports. The Committee is also indebted to Dr. Geoffrey Sunshine for assistance in preparing its Commentary, and to Ms.Virgi Hepner, Mrs. Valerie Kelleher, Ms. Malti Sharma, and Ms. Mary Stilwell for their roles in publishing this report.

REFERENCES

Abbey DE, Mills PK, Petersen FF, Beeson L. 1991a. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh Day Adventists. Environ Health Perspect 94:43–50.

Abbey DE, Moore J, Petersen F, Beeson L. 1991b. Estimating cumulative ambient ozone concentrations of air pollutants: Description and precision of methods used for an epidemiologic study. Arch Environ Health 46:281–287.

Abbey DE, Petersen F, Mills PK, Beeson WL. 1993. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. Arch Environ Health 48:33–46.

American Thoracic Society. 1991. Lung function testing: Selection of reference values and interpretative strategies. Am Rev Respir Dis 144:1202–1218.

Balmes JR, Chen LL, Scanell C, Tager IB, Christan D, Hearne PQ, Kelly T, Aris RM. 1996. Ozone-induced decrements in FEV_1 and FVC do not correlate with measures of inflammation. Am J Respir Crit Care Med 153:904–909.

Balmes JR, Aris RM, Chen LL, Scanell C, Tager IB, Finkbeiner W, Christian D, Kelly T, Hearne PQ, Ferrando R, Welch B. 1997. Effects of Ozone on Normal and Potentially Sensitive Human Subjects. Part I: Airway Inflammation and Responsiveness to Ozone in Normal and Asthmatic Subjects. Research Report Number 78. Health Effects Institute, Cambridge, MA.

Boorman GA, Schwartz LW, Dungworth DL. 1980. Pulmonary effects of prolonged ozone insult in rats: Morphometric evaluation of the central acinus. Lab Invest 43:108–115.

Catalano PJ, Chang L-Y, Harkema JR, Kaden DA, Last JA, Mellick PW, Parks WC, Pinkerton KE, Radhakrishnamurthy B, Ryan LM, Szarek JL. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part XI: Integrative Summary. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Chang L-Y, Huang J, Stockstill BL, Graham JA, Grose EC, Ménache MG, Miller FJ, Costa DL, Crapo JD. 1992. Epithelial injury and interstitial fibrosis in the proximal alveolar regions of rats chronically exposed to a simulated pattern of urban ambient ozone. Toxicol Appl Pharmacol 115:241–252.

Chang L-Y, Stockstill BL, Ménache M, Mercer RM, Crapo JD. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part VIII: Morphometric Analysis of Structural Alterations in Alveolar Regions. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Cochrane GM, Prieto F, Clark TJH. 1977. Intrasubject variability of maximal expiratory flow volume curve. Thorax 32:171–176.

Contant CF, Stock TH, Buffler PA, Holguin AH, Gehan BM. 1987. The estimation of personal exposures to air pollutants for a community-based study of health effects in asthmatics: Exposure model. J Air Pollut Control Assoc 37:587–594.

Costa DL, Tepper JS, Stevens MA, Watkinson WP, Doerfler DL, Gelzleichter TR, Last JA. 1995. Restrictive lung disease in rats exposed chronically to an urban profile of ozone. Am J Respir Crit Care Med 151:1512–1518.

Detels R, Tashkin D, Sayre J, Rokaw SN, Coulson AH, Massey FJ Jr, Wegman DH. 1987. The UCLA Population Studies of Chronic Obstructive Respiratory Disease. 9. Lung function changes associated with chronic exposure to photochemical oxidants: A cohort study among never-smokers. Chest 92:594–603.

Detels R, Tashkin D, Sayre J, Rokaw SN, Massey FJ Jr, Coulson AH, Wegman DH. 1991. The UCLA Population Studies of Chronic Obstructive Respiratory Disease. X. A cohort study of changes in respiratory function associated with chronic exposure to SO_x, NO_x and hydrocarbons. Am J Public Health 81:350–359.

Druzik JR, Adams MS, Tiller C, GR Cass. 1989. The measurement and model predictions of indoor ozone concentrations in museums. Atmos Environ 7:1814–1823.

Federal Register. 1971. National primary and secondary ambient air quality standards. Fed Reg 36:8186–8201.

Federal Register. 1997. National Ambient Air Quality Standards for Ozone: Final Rule. Fed Reg 62:1–37 40 CFR Part 50 July 18, 1997.

Folinsbee LJ, McDonnell WF, Horstmann DH. 1988. Pulmonary function and symptom responses after 6.6 hour exposure to 0.12 ppm ozone with moderate exercise. J Air Pollut Control Assoc 38:28–35.

Frampton MW, Balmes JR, Cox C, Krein PM, Speers DM, Tsai Y, Utell MJ. 1997. Effects of Ozone on Normal and Potentially Sensitive Human Subjects. Part II: Airway Inflammation and Responsiveness to Ozone in Nonsmokers and Smokers. Research Report Number 78. Health Effects Institute, Cambridge, MA.

Fujinaka LE, Hyde DM, Plopper CG, Tyler WS, Dungworth DL, Lollini LO. 1985. Respiratory bronchiolitis following long-term ozone exposure in bonnet monkeys: A morphometric study. Exp Lung Res 8:167–190.

Gong H, Bradley PW, Simmons MS, Tashkin DP. 1986. Impaired exercise performance and pulmonary function in elite cyclists during low-level ozone exposure in a hot environment. Am Rev Respir Dis 134:726–733.

Harkema JR, Mauderly JL. 1994. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part V: Effects on Pulmonary Function. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Hayes GB, Christiani DC. 1993. Measures of small airways disease as predictors of chronic obstructive pulmonary disease. Occup Med 8:375–395.

Hayes SR. 1991.Use of an indoor air quality model (IAQM) to estimate indoor ozone levels. J Air Waste Manage Assoc 41:161–170.

Hazucha MJ. 1987. Relationship between ozone exposure and pulmonary function changes. J Appl Physiol 62:1671–1680.

Health Effects Institute. 1994. Environmental Epidemiology Planning Project. HEI Communication Number 3. Health Effects Institute, Cambridge, MA.

Keefe M, Bennett W, Dewitt P, Seal E, Strong A, Gerritty T. 1991. The effect of ozone exposure on the dispersion of inhaled aerosol boluses in healthy human subjects. Am Rev Respir Dis 144:23–30.

Kinney PL, Özkaynak H. 1991. Associations of daily mortality and air pollution in Los Angeles County. Environ Res 54:99–120.

Koren H, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DH, Kozumbo WJ, Becker S, House DE, McDonnell WF, Bromberg PA. 1989. Ozone-induced inflammation in the lower airways of human subjects. Am Rev Respir Dis 139:407–415.

Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. 1997. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen: Results of a pilot study. Environ Res 72:8–23.

Last JA, Gelzleichter TR, Harkema JR, Hawk S. 1994. Consequences of Prolonged Inhalation of Ozone on Fischer-344/N Rats: Collaborative Studies. Part I: Content and Cross-Linking of Lung Collagen. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Liu L-J S, Delfino R, Koutrakis P. 1997. Ozone exposure assessment in a southern California community. Environ Health Perspect 105:58–65.

Miller FJ, Overton JH Jr, Jaskot RH, Menzel DB. 1985. A model of the regional uptake of gaseous pollutants in the lungs. I: The sensitivity of the uptake of ozone in the human to lower respiratory tract secretions and exercise. Toxicol Appl Pharmacol 79:11–27.

National Heart, Lung and Blood Institute. 1973. Suggested Standardized Procedures for Closing Volume. Division of Lung Diseases, National Heart, Lung and Blood Institute, Bethesda, MD.

Overton JH Jr, Graham RC. 1989. Predictions of ozone absorption in humans from newborn to adult. Health Phys [Suppl] 57 (1):29–36.

Pinkerton KE, Ménache M, Plopper CG. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part IX: Changes in the Tracheobronchial Epithelium, Pulmonary Acinus, and Lung Antioxidant Enzyme Activity. Research Report Number 65. Health Effects Institute, Cambridge, MA.

Scanlon PD, Hankinson J. 1996. Physiologic methods. In: Occupational and Environmental Respiratory Disease (Harber P, Schenker MB, Balmes JR, eds.) pp. 39–54. Mosby Yearbook, St. Louis, MO.

Schmitzberger R, Rhomberg K, Büchele H, Puchegger R, Schmitzberger-Natzmer D, Kemmler G, Panosch B. 1993. Effects of air pollution on the respiratory tract of children. Pediatr Pulmonol 15:68–74.

Stern B, Raizenne M, Burnett R, Jones L, Kearney J, Franklin J. 1994. Air pollution and childhood respiratory health: Exposure to sulphate and ozone in ten Canadian rural communities. Environ Res 66:125–142.

Torres A, Utell MJ, Morow PE, Voter KZ, Whitin JC, Cox C, Looney RJ, Speers DM, Tsai Y, Frampton MW. 1997. Airway inflammation in nonsmokers and smokers with varying responsiveness to ozone. Am J Respir Crit Care Med 156:728–736.

U.S. Environmental Protection Agency. 1996a. Air Quality Criteria for Ozone and Related Photochemical Oxidants. EPA/600/P-93/004cF. Office of Research and Development, Washington, DC.

U.S. Environmental Protection Agency. 1996b. Review of National Ambient Air Quality Standards for Ozone: Assessment of Scientific and Technical Information. OAQPS Staff Paper. EPA-452/R-96-007. Office of Air Quality Planning and Standards, Research Triangle Park, NC.

Vollmer WM, McCamant LE, Johnson LR, Buist AS. 1990. Long-term reproducibility of tests of small airways function Comparisons with spirometry. Chest 98:303–307.

Wechsler CJ, Shields HC, Naik DV. 1989. Indoor ozone exposures. J Air Pollut Control Assoc 39:1562–1568.

Weinmann GG,Weidenbach-Gerbase M, Foster WM, Zacur H, Frank R. 1995. Evidence for ozone-induced small-airway dysfunction: Lack of menstrual-cycle and gender effects. Am J Respir Crit Care Med 152:988–996.

Wright JL, Cagle P, Churg A, Colby TV, Myers J. 1992. State of the art: Diseases of the small airways. Am Rev Respir Dis 146:240–262.

Yocum JE. 1982. Indoor-outdoor air quality relationships: A critical review. J Air Pollut Control Assoc 32:500–520.

RELATED HEI PUBLICATIONS: DOSIMETRY AND HUMAN RESPONSES TO OZONE

Report No.	Title	Principal Investigator	Publication Date
Research Reports			
14	The Effects of Ozone and Nitrogen Dioxide on Lung Function in Healthy and Asthmatic Adolescents	J.Q. Koenig	1988
39	Noninvasive Determination of Respiratory Ozone Absorption: Development of a Fast-Responding Ozone Analyzer	J.S. Ultman	1991
63	Development of Samplers for Measuring Human Exposures to Ozone		1994
	Active and Passive Ozone Samplers Based on a Reaction with a Binary Reagent	J.D. Hackney	
	A Passive Ozone Sampler Based on a Reaction with Nitrite	P. Koutrakis	
	A Passive Ozone Sampler Based on a Reaction with Iodide	Y. Yanagisawa	
69	Noninvasive Determination of Respiratory Ozone Absorption: The Bolus-Response Method	J.S. Ultman	1994
70	Oxidant and Acid Aerosol Exposure in Healthy Subjects and Subjects with Asthma		1994
	Part I: Effects of Oxidants, Combined with Sulfuric or Nitric Acid, on the Pulmonary Function of Adolescents with Asthma	J.Q. Koenig	
	Part II: Effects of Sequential Sulfuric Acid and Ozone Exposures on the Pulmonary Function of Healthy Subjects and Subjects with Asthma	M.J. Utell	
75	Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis	D.P. Loomis	1996
78	Effects of Ozone on Normal and Potentially Sensitive Human Subjects		1997
	Part I: Airway Inflammation and Responsiveness to Ozone in Normal and Asthmatic Subjects	J.R. Balmes	
	Part II: Airway Inflammation and Responsiveness to Ozone in Nonsmokers and Smokers	M.W. Frampton	
	Part III: Mediators of Inflammation in Bronchoalveolar Lavage Fluid from Nonsmokers, Smokers, and Asthmatic Subjects Exposed to Ozone: A Collaborative Study	M.W. Frampton and J.R. Balmes	
79	Improvement of a Respiratory Ozone Analyzer	J.S. Ultman	1997
HEI Communications			
3	Environmental Epidemiology Planning Project [Section on Tropospheric Ozone]		1994
	Introduction	I.B. Tager	
	Use of Human Lung Tissue for Studies of Structural Changes Associated with Chronic Ozone Exposure: Opportunities and Critical Issues	M. Lippmann	
	Examining Acute Health Outcomes Due to Ozone Exposure and Their Subsequent Relationship to Chronic Disease Outcomes	B.D. Ostro	
	Detection of Chronic Respiratory Bronchiolitis in an Oxidant-Exposed Population: Analogy to Tobacco Smoke Exposure	D. Bates	
	The Role of Ozone Exposure in the Epidemiology of Asthma	J.R. Balmes	
	Identification of Subpopulations That Are Sensitive to Ozone Exposure: Use of End Points Currently Available and Potential Use of Laboratory-Based End Points Under Development	R.B. Devlin	
	Design and Analysis of Studies of the Health Effects of Ozone	A. Munoz	
	Summary of Papers and Research Recommendations of Working Group on Tropospheric Ozone	I.B. Tager	

A list of HEI Research Reports on ozone toxicity in animals and in vitro models, or copies of the reports listed above can be obtained by writing or calling the Health Effects Institute, 955 Massachusetts Avenue, Cambridge, MA 02139. Phone (617) 876-6700 FAX (617) 876-6709 E-mail pubs@healtheffects.org http://www.healtheffects.org

HEI

The Board of Directors

Health Research Committee

Health Review Committee

Officers and Staff

HEI HEALTH EFFECTS INSTITUTE 955 Massachusetts Avenue, Cambridge, MA 02139 (617) 876-6700

Research Report Number 81

March 1998