HEI HEALTH EFFECTS INSTITUTE

Nitrogen Dioxide and Respiratory Illness in Children

Part I: Health Outcomes

Jonathan M. Samet, William E. Lambert, Betty J. Skipper, Alice H. Cushing, William C. Hunt, Stephen A. Young, Leroy C. McLaren, Margo Schwab, and John D. Spengler

Part II: Assessment of Exposure to Nitrogen Dioxide

William E. Lambert, Jonathan M. Samet, William C. Hunt, Betty J. Skipper, Margo Schwab, and John D. Spengler

Departments of Medicine, Pediatrics, Microbiology, and Family and Community Medicine, and New Mexico Tumor Registry, Cancer Center, University of New Mexico Medical Center, Albuquerque, NM, and Department of Environmental Health, Harvard School of Public Health, Boston, MA

Includes the Commentary of the Institute's Health Review Committee

Research Report Number 58
June 1993

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 materials), and unregulated pollutants (such as diesel engine exhaust, methanol, and aldehydes). To date, HEI has supported more than 120 projects at institutions in North America and Europe.

Typically, HEI receives half its funds from the Environmental Protection Agency and half from 28 manufacturers and marketers of motor vehicles and engines in the United States. Occasionally, grants from other public or private organizations support special projects. For this study, the Institute acknowledges the significant support of the Gas Research Institute. However, in all cases HEI exercises complete autonomy in setting its research priorities and in disbursing its funds. An independent Board of Directors governs HEI. The Institute's Research Committee and the Review Committee 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 Investigator's Report and the Review Committee's evaluation of the work's scientific and regulatory relevance.

HEI Statement

Synopsis of Research Report Number 58: Parts I and II

Nitrogen Dioxide and Respiratory Illness in Children

BACKGROUND

Nitrogen dioxide, a common indoor and outdoor air pollutant, is a by-product of high-temperature combustion. Motor vehicles and power plants are primarily responsible for the nitrogen dioxide in outdoor air. The U.S. Environmental Protection Agency, which establishes National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide and other air pollutants, has set the NAAQS for nitrogen dioxide as an annual average of 53 parts per billion (ppb) (100 $\mu g/m^3$). Although the annual average concentrations of nitrogen dioxide are well below 50 ppb in most regions of the United States, the standard is exceeded in areas of southern California, and short-term peaks of 100 ppb, and occasionally 200 ppb, occur in urban areas.

Indoor levels of nitrogen dioxide are often higher than outdoor concentrations, especially in homes where there are unvented heating and cooking appliances that utilize natural gas, kerosene, coal, or wood. Such exposures are of concern because some studies suggest that children exposed to nitrogen dioxide have more respiratory illnesses than those who are not exposed.

Although mild respiratory illnesses in infants and young children are quite common, more serious illnesses can be life-threatening and might increase the risk of developing lung disease later in life. The epidemiologic studies that have examined the role of nitrogen dioxide in childhood respiratory disease have produced inconsistent results, partly because of the difficulty of assessing exposures and measuring respiratory illness in a community setting. This study was conducted to address the limitations of previous studies and to help resolve whether exposure to nitrogen dioxide increases the incidence or duration, or both, of respiratory illness in infants.

APPROACH

Drs. Jonathan M. Samet, John D. Spengler, and colleagues conducted a prospective investigation of 1,205 healthy infants living in homes with gas or electric stoves in Albuquerque, NM. Nitrogen dioxide exposures were carefully estimated from repeated measurements in multiple locations in the subjects' homes throughout the entire 18-month observation period. Respiratory illnesses were monitored prospectively using a surveillance system based on daily parental diaries of respiratory signs and symptoms. Parental reports of illness episodes were validated in a subset of the population by comparison with clinical diagnoses and microbiological testing. Potential confounding factors that influence respiratory infections were reduced by selecting subjects whose parents did not smoke or intend to use day-care services outside the home. Rigorous quality assurance procedures were implemented in all phases of the experimental protocol.

RESULTS

The investigators found no association between nitrogen dioxide exposure and the incidence rates for any illness category (upper respiratory illness, lower respiratory illness, lower respiratory illness with wet cough, and lower respiratory illness with wheeze); nor was there any association between illness incidence and the presence of a gas stove. There was also no significant association between nitrogen dioxide levels and the duration of illness for the first three illness categories listed above. However, at the highest nitrogen dioxide exposure category (greater than 40 ppb), there was a nonsignificant increase in the duration of illnesses classified as lower respiratory illness with wheezing. These findings apply to healthy infants, and cannot be generalized to populations who may be more susceptible to the effects of nitrogen dioxide exposure, such as premature babies, babies with low birth weight or respiratory problems, and infants living in homes with parents who smoke. These findings also cannot be generalized to older children or adults.

A key consideration in interpreting these results is the level of nitrogen dioxide to which the children were exposed. The mean nitrogen dioxide levels in the infants' bedrooms in homes with gas stoves were 21 ppb during the winter and 14 ppb in the summer. The mean nitrogen dioxide level in bedrooms of homes with electric stoves was 7 ppb during both seasons. Over 75% of the measured nitrogen dioxide concentrations were less than 20 ppb; 5% were greater than 40 ppb. These levels, although similar to levels observed in many locations in the United States, are lower than nitrogen dioxide concentrations in heavily polluted cities and in poorly ventilated inner-city apartments. Thus, the study results cannot be generalized to infants or toddlers exposed to levels of nitrogen dioxide substantially in excess of 40 ppb.

The investigators' observations are important because they indicate that in a population of healthy infants and toddlers, no significant associations between nitrogen dioxide exposure (in the range of 0 to 40 ppb) and respiratory illness were found when every precaution was taken to make an accurate assessment of the pollutant exposures, to validate the measurements of respiratory illness, to eliminate potentially confounding variables such as exposure to environmental tobacco smoke, and to adjust for the variables that could not be eliminated.

This Statement is a summary, prepared by the Health Effects Institute (HEI) and approved by the Board of Directors, of a research project sponsored by HEI from 1987 to 1992. This study was conducted by Dr. Jonathan M. Samet and colleagues of the School of Medicine at the University of New Mexico and Dr. John D. Spengler and associates of the Harvard School of Public Health. Support for this study came from HEI, whose funding in this instance was derived from the U.S. Environmental Protection Agency, 28 motor vehicle manufacturers, and the Gas Research Institute. The following Research Report contains Part I and Part II of the Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

Library of Congress Catalog No. 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, and 51 excepted. Reports 1 through 20, 25, 26, 32, and 51 are printed on acid-free coated paper.

TABLE OF CONTENTS

HEI Research Report Number 58

Nitrogen Dioxide and Respiratory Illness in Children

(continued on next page)

Nitrogen Dioxide and Respiratory Illness in Children

Part I: Health Outcomes

Jonathan M. Samet, William E. Lambert, Betty J. Skipper, Alice H. Cushing, William C. Hunt, Stephen A. Young, Leroy C. McLaren, Margo Schwab, and John D. Spengler

ABSTRACT

We have carried out a prospective cohort study to test the hypothesis that exposure to nitrogen dioxide increases the incidence and severity of respiratory infections during the first 18 months of life. Between January 1988 and June 1990, 1,315 infants were enrolled into the study at birth and followed with prospective surveillance for the occurrence of respiratory infections and monitoring of nitrogen dioxide concentrations in their homes. The subjects were healthy infants from homes without smokers; they were selected with stratification by type of cooking stove at a ratio of four to one for gas and electric stoves. Illness experience was monitored by a daily diary of symptoms completed by the mother and a telephone interview conducted every two weeks. Illnesses with wheezing or wet cough were classified as involving the lower respiratory tract; all other respiratory illnesses were designated as involving the upper respiratory tract. Exposure to nitrogen dioxide was estimated by two-week average concentrations measured in the subjects' bedrooms with passive samplers.

This analysis is limited to the 1,205 subjects completing at least one month of observation; of these, 823 completed the full protocol, contributing 82.8% of the total number of days during which the subjects were under observation. Incidence rates for all respiratory illnesses, all upper respiratory illness, all lower respiratory illnesses, and lower respiratory illness further divided into those with any wheezing, or wet cough without wheezing, were examined within strata of nitrogen dioxide exposure at the time of the illness, nitrogen dioxide exposure during the prior month, and type of cooking stove. Consistent trends of increasing illness incidence rates with increasing exposure to nitrogen dioxide were not evident for either the lagged or unlagged exposure variables. The effect of nitrogen dioxide exposure on illness occurrence during at-risk intervals of two weeks' duration was examined using the generalized estimating equation approach. In these multivariate analyses, none of the odds ratios was significantly elevated for unlagged nitrogen dioxide exposures, lagged nitrogen dioxide exposures, or stove type. Duration of illness was assessed in relation to the same exposure variables; illness duration and nitrogen dioxide exposure were not associated.

We have found that indoor exposure to nitrogen dioxide is associated with neither the incidence nor the duration of respiratory illnesses. The study was designed to have sufficient power to detect effects of nitrogen dioxide exposure of magnitudes previously reported and in a range relevant to public health concern; the lack of association cannot be attributed to potential bias from misclassification of outcome or exposure. The extent to which the findings can be generalized is limited by the selection of healthy infants who were not exposed to parental smoking at home. However, the findings of the study can be extended to homes with gas stoves in the many regions of the United States where the outdoor air is not heavily polluted by nitrogen dioxide. In extending the findings to nitrogen dioxide in outdoor air, consideration should be given to differences in the chemical species of nitrogen oxides in indoor and outdoor air.

INTRODUCTION

Nitrogen dioxide (NO_2)* is an oxidant gas that contaminates ambient air in many urban and industrial loca-

This study was supported by funds from the U.S. Environmental Protection Agency, the motor vehicle industry, and the Gas Research Institute. This Investigators' Report is Part I of the Health Effects Institute's Research Report Number 58, which also includes Part II (an Investigators' Report by Lambert and colleagues), a Commentary on both Investigators' Reports by the HEI Health Review Committee, and an HEI Statement about the research project.

Correspondence regarding the Investigators' Report by Dr. Samet and associates may be addressed to Dr. Jonathan M. Samet, Professor of Medicine, New Mexico Tumor Registry, University of New Mexico Medical Center, 900 Camino de Salud NE, Albuquerque, NM 87131-5306.

Part of this work is presented in "Nitrogen Dioxide and Respiratory Illnesses in Infants," by JM Samet, WE Lambert, BJ Skipper, AH Cushing, WC Hunt, SA Young, LC McLaren, M Schwab, JD Spengler, American Review of Respiratory Disease, Vol. 148, 1993, and is being published with license from the copyright holder and is not for reproduction.

* A list of abbreviations appears at the end of this report for your reference.

tions and indoor air in homes with unvented combustion appliances. The U.S. Environmental Protection Agency presently regulates NO_2 in ambient air as a "criteria" pollutant; the standard currently in place sets the maximum annual average concentration outdoors as 53 parts per billion (ppb). In spite of decades of laboratory, clinical, and epidemiological research, however, the health effects of inhaled NO_2 are not yet fully understood. Nitrogen dioxide is known to cause lung damage at high concentrations (National Research Council 1976), but effects at levels currently measured in outdoor and indoor air in the United States have been difficult to characterize.

The toxicological evidence suggests that increased susceptibility to infection is one potential concern (Samet and Utell 1990; Samet 1991). In experimental models, NO_2 reduces the efficacy of lung defense mechanisms; effects on mucociliary clearance, the alveolar macrophage, and the immune system have been demonstrated (National Research Council 1976; Morrow 1984; Pennington 1988). In animal experiments involving challenge with respiratory pathogens, exposure to NO_2 reduces the clearance of infecting organisms and increases mortality. Epidemiologic studies have assessed NO_2 exposure in indoor and outdoor air as a risk factor for respiratory infection. Because of difficult methodologic problems, the results of these studies have not provided definitive human evidence linking NO_2 and respiratory infection (Pennington 1988; Samet and Utell 1990).

SPECIFIC AIMS

The goal of this prospective cohort study was to test the hypothesis that exposure to NO_2 increases the incidence and severity of respiratory infections in infants during the first 18 months of life (Samet et al. 1992). The study was conducted in Albuquerque, NM, where outdoor levels of NO_2 are generally low, and emissions from gas ranges and ovens and other unvented combustion appliances are the principal sources of exposure (Harlos et al. 1987; Marbury et al. 1988; Samet and Spengler 1989). Between January 1988 and June 1990, 1,315 infants were enrolled in the study at birth and followed with prospective surveillance for the occurrence of respiratory infections, as assessed by maternal reports of symptoms and monitoring of NO_2 concentrations in their homes. The study, which is based on extensive pilot research (Harlos et al. 1987; Marbury et al. 1988; Samet and Spengler 1989), was designed to address the potential limitations of misclassification of illness and exposure, confounding, and inadequate statistical power. This report describes the relation between NO_2 exposure and the incidence of respiratory illnesses; it also addresses NO_2 exposure and the duration of respiratory illnesses. The exposure data are described in detail in the accompanying report, Part II: Assessment of Exposure to Nitrogen Dioxide (Lambert et al. 1993).

The specific objectives of the study were:

1. To enroll a cohort of infants and follow them prospectively from birth through 18 months of life to ascertain respiratory illnesses using diaries and surveillance telephone calls, and to assess exposures to NO_2 using passive samplers;
2. To measure NO_2 concentrations continuously in the kitchen, family activity room, and index subject's bedroom in a sample of homes; and
3. To compare the classification of illness by the surveillance system with the results of viral cultures, diagnoses made by nurse practitioners, and diagnoses made by the subjects' physicians.

MATERIALS AND METHODS

STUDY DESIGN

The study was a prospective cohort investigation designed to test the hypothesis that indoor exposure to NO_2 during the first 18 months of life increases the incidence and severity of lower respiratory illnesses (Samet et al. 1992). Subjects were enrolled at birth and followed prospectively with measurement of NO_2 and surveillance for respiratory illnesses. To increase the number of subjects at the higher end of the distribution of NO_2 exposure, the subjects were selected from households with gas and electric cooking stoves at a target ratio of four to one.

SUBJECT SELECTION

Potential subjects were identified at birth primarily by screening of deliveries for healthy live births at all Albuquerque hospitals. Infants requiring intensive care, low-birth-weight and premature infants, and infants with major congenital anomalies were excluded by record review; infants not residing within metropolitan Albuquerque also were excluded. Mothers of normal infants were approached in their hospital rooms and asked a brief series of questions to establish eligibility. Criteria for selection included having a nonsmoking mother and no other family members smoking inside the home, the parents' intention of caring for the child at home, telephone in the residence, and mother above 18 years of age who speaks English and had

no plans to move away from Albuquerque. Infants with exposure to tobacco smoking at home were excluded to limit potential confounding and effect modification by involuntary smoking, which is associated with lower respiratory illnesses in the first two years of life (U.S. Department of Health and Human Services 1986). The sample was restricted to infants whose mothers intended to keep them at home in order to reduce misclassification of exposure by time spent outside of the home and to reduce potential confounding by day-care attendance. At the beginning of the study, a small number of subjects was recruited from physicians' offices. Enrollment began in January 1988 and was completed in June 1990.

OBSERVATION OF SUBJECTS

Subjects were observed from enrollment through 18 months of age, or until they became ineligible by spending more than 20 hours per week in day care, moving away from Albuquerque, or having an adult household member begin to smoke cigarettes in the home. Subjects were also released on the basis of refusal or noncompliance with study procedures. Time periods of seven days or more spent away from the home were documented.

DATA COLLECTION

Household Characterization

At an initial home visit, a field technician completed a questionnaire and performed a survey to obtain information on cooking appliances, heating systems (including fireplaces, woodstoves, and kerosene space heaters), cooling systems, house construction and size, other potential sources of air contaminants, and the use of air cleaning devices. The field technician also instructed the parents (generally the mother) on the placement of the passive diffusion samplers (Palmes tubes) (Palmes et al. 1976) used to measure NO_2 and documented the tube locations on diagrams. At the midpoint of the 18-month observation interval and on completion of the study, any changes in household characteristics, cooking and heating equipment, and other potential sources of indoor air pollution were documented. Changes in these characteristics were also documented whenever a subject changed residences.

Information was also obtained on the household composition, household income, sources of medical care for the subject, and the availability of health insurance for the subject. Demographic data collected included the race and ethnicity of the parents and the years of education completed by the mother and father. For all family members, a questionnaire covered the presence of major respiratory and allergic illnesses. Additionally, both parents were asked to complete the standardized respiratory symptoms questionnaire developed by the American Thoracic Society (Ferris 1978).

Assessment of Day-Care Attendance and Breast Feeding

In surveillance calls made every two weeks, information was obtained on the number of hours of day-care attendance during the one week before the call. Breast feeding during the two previous weeks was characterized as none, partial, or full, referring to the extent to which breast feeding was the source of milk.

Nitrogen Dioxide Exposure Assessment

Two-week integrated concentrations of NO_2 were obtained with passive diffusion tubes (Palmes et al. 1976). A complete description of the tubes, the field monitoring protocol, the laboratory analysis, the approach for estimating personal exposure, and the quality assurance and quality control program is provided in Part II of this report by Lambert and associates (1993). In brief, the monitoring protocol for each home varied with the type of stove and the season. In homes with gas stoves, the subjects' bedrooms were monitored every two weeks, year-round; during the colder seasons, additional two-week measurements were made every other month in the kitchen and activity room. In homes with electric stoves, the child's bedroom was monitored year-round during every other two-week cycle. Consecutive two-week measurements of outdoor concentrations were obtained at 11 monitoring sites maintained by the City of Albuquerque.

The time series of NO_2 measurements for each residence was reviewed to identify extreme values and to apply exclusion criteria based on the known performance characteristics of the sampler tubes and the seasonal distributions of measurements available for each home. Gaps arose in the series of NO_2 measurements because of the sampling protocol for electric stove homes, time people spent away from home, excluded values, and lost or improperly handled tubes. In homes with gas stoves, 8% of the total number of days under observation were missing NO_2 measurements; likewise, 48% of the total number of days under observation were missing NO_2 measurements for homes with electric stoves. The median number of days without NO_2 data was 33 days for subjects from homes with gas stoves and 188 days for subjects from homes with electric stoves. These gaps were covered by straight-line interpolation from the bounding measurements.

Daily exposures of the infants to NO_2 were estimated by the bedroom concentration. Estimates of exposure based on

bedroom concentration were tightly correlated with estimates of exposures calculated as time-weighted averages of the concentrations in the kitchen, bedroom, and activity room (Harlos et al. 1987; see Part II, Lambert et al. 1993).

Transient exposures to elevated levels of NO_2 generated during cooking have been considered as making a potentially significant contribution to the personal exposures of infants (Samet and Utell 1990). To characterize the variation of NO_2 levels in homes with gas cooking ranges, we deployed continuous monitoring instrumentation (Odyssey 2000 NO_2 Analyzer, Transducer Research, Naperville, IL). A set of three monitors was placed in each of 70 homes with gas cooking stoves or kerosene space heaters, with one in the child's bedroom, another in the activity room, and the third in the kitchen. Results from the continuous monitoring for NO_2 using these monitors will be reported in a later part of this report.

As a potential measure of peaks of exposure generated during cooking, stove use was assessed during the surveillance telephone calls made every two weeks. The questionnaire covered stove usage during the previous 24 hours. Additionally, as a basis for estimating the child's total personal exposure from microenvironments in the home, time-activity information was obtained every two months by telephone.

Respiratory Illness Assessment

The surveillance method for respiratory illnesses was modeled on the approach used in the Tecumseh study by Monto and colleagues (1971) and adapted as a result of the experience gained during our pilot study (Samet and Spengler 1989). Mothers were given a calendar diary and asked to record for each day the presence of respiratory symptoms and signs, including runny or stuffy nose, dry cough, wet cough, trouble with breathing, and other symptoms and signs including trouble feeding, rash, and fever. The mother also recorded times she considered the child to be ill. At the time of enrollment, the mothers were instructed in the use of the calendar diary by either of two nurses who fulfilled this role throughout the investigation.

Every two weeks, the mother was telephoned and asked about symptoms and any illnesses. In a standard series of questions, the mother was asked to review the calendar diary and to report all symptoms and any illnesses since the last telephone call. If respiratory symptoms were reported for the child, information was obtained on physician visits, diagnoses made by the physician, and any medication that had been prescribed. For a sample of the ill children, a nurse practitioner made a home visit to conduct a standardized history and physical assessment (Samet et al. 1992). Outpatient records at selected Albuquerque outpatient facilities were reviewed for a majority of the subjects. Elsewhere, we have reported on the comparability of the parental reports with the clinical evaluations by the project nurse practitioners and the subjects' health care providers (Samet et al. 1993).

With the surveillance reports, illness events were defined as the occurrence of at least two consecutive days of any of the following: runny or stuffy nose, wet cough, dry cough, wheezing, or trouble with breathing. Wheezing refers to a high-pitched musical sound audible during breathing; trouble with breathing was the parents' perception of rapid or labored breathing. The illness events ended with two consecutive symptom-free days. The illness events were further classified as follows:

Upper respiratory tract: At least two consecutive days of any combination of runny or stuffy nose, dry cough, and trouble breathing.

Lower respiratory tract: At least two consecutive days of any of the upper respiratory symptoms plus wet cough or wheezing or both being reported on at least one day.

Lower respiratory tract, wet cough: Any illness meeting the criteria for lower respiratory tract but without wheezing at any time.

Lower respiratory tract, wheezing: Any illness meeting the criteria for lower respiratory tract with wheezing reported for at least one day.

Illness duration was calculated as the number of days from onset of symptoms to the last day with symptoms before the occurrence of two consecutive symptom-free days.

Comparing this symptom-based illness classification method with the diagnoses made by the project nurse practitioners and by the subjects' health care providers showed that the telephone surveillance system was sensitive to but nonspecific for detecting lower respiratory illnesses diagnosed by clinicians (Samet et al. 1993). (Sensitivity refers to the proportion of clinician-diagnosed lower respiratory illnesses similarly classified by the surveillance system; specificity is the proportion of illnesses not classified by the physician as lower respiratory that were similarly classified by the surveillance system.) In comparison with the diagnoses made by a nurse practitioner, parents' reports of wet cough or wheezing were sensitive (93.4%) for detecting lower respiratory illnesses but nonspecific, with specificity of only 24.4%. The majority of the lower respiratory illnesses classified as false-positive in relation to the clinician diagnoses had the symptom of wet cough. The comparison of parents' reports with outpatient records provided similar findings. Based on this comparison of the classification of illnesses by the surveillance system with clinicians' diag-

noses, we have further stratified the category of lower respiratory illnesses into those with wet cough alone and those with wheezing in all analyses of the effect of NO_2.

QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and control procedures were implemented wherever possible. Standard operating protocols documented all procedures, and the training and capabilities of all staff were recorded. Weekly quality assurance meetings were held in Albuquerque, and an outside auditor, contracted by the funding agency, provided quality assurance for both the Albuquerque and Harvard School of Public Health groups. The external quality assurance report for the study is included as Appendix C.

The protocol for measuring NO_2 incorporated replicates for 5% of field samples and field blanks. At the Harvard School of Public Health, a statistical quality control check was made on all measurements and listed exceptions for evaluation. During home visits for illness evaluation, the nurse practitioner checked on the mother's compliance with proper placement of the Palmes tubes and checked on the use of the calendar-diary to record the subject's symptoms. In a sample of homes included in a special project, concentrations measured by technician-placed tubes were compared with parent-placed tubes during two-week periods of the winter and summer. On a sample of the nurse practitioner's visits to the homes, an experienced pediatrician performed a parallel assessment. Data were keyed with verification and carefully edited for internal consistency. Samples of original and keyed data were reviewed on a weekly basis to identify any problems, and the data were reviewed approximately annually by the external auditor.

DATA ANALYSIS

Calculation of Incidence Rates

In calculating incidence rates of respiratory illness, days at risk were those days of observation during which an illness was not in progress. Because subjects were at risk of illness following two symptom-free days, accrual of days at risk of illness began on the third day after enrollment. After an illness or after any period of seven days or more spent outside the home without health surveillance, counting of days at risk similarly began after two symptom-free days. These mandatory two-day intervals were not included in the days at risk. Incidence rates of the several types of illness were calculated as the ratio of the number of illness events to the number of days at risk, and annualized to 365 days at risk. By definition, days with a lower respiratory illness in progress were excluded from the days at risk for an upper respiratory illness. Confidence limits for the rates were calculated using an estimate of the standard error based on the Poisson distribution (Breslow and Day 1987).

Multivariate Analysis

Multivariate methods were used to control for potential confounding factors and to test for effect modification. In analyses of determinants of incident illnesses, the outcome variable was the occurrence of illness during two-week intervals of days at risk. The two-week period was chosen because of its correspondence with the averaging time for the NO_2 measurements and the rarity of multiple illnesses during intervals of this length. The unlagged NO_2 exposure category assigned to the interval was the 14-day average centered on the first day of the interval; the lagged exposure category corresponded to the average of the unlagged NO_2 for the previous two two-week blocks. Other time-varying covariates (age, day-care attendance, breast feeding, and season) were assigned the values associated with the first day.

The independent variables considered in the multivariate analyses included the fixed factors of birth order (first born versus other), gender, ethnicity (Hispanic versus non-Hispanic), parental asthma and atopic status (considered positive if hay fever or desensitization shots were reported), household income (less than $10,000, $10,000 to $40,000, or greater than $40,000), and maternal education (12 years or less, 13 to 15 years, or 16 years or more). Other variables considered were the temporally varying factors of age (6 months or less, 7 to 12 months, or 13 to 18 months), calendar month, day-care attendance (none, 1 to 4 hours, or 5 or more hours per week), and breast feeding (none, partial, or full). Indicator variables were created for six two-month blocks of the year, defined as December through January, February through March, April through May, June through July, August through September, and October through November, on the basis of illness incidence patterns. Additionally, an index of maternal tendency to report respiratory symptoms was created as the sum of the number of positive responses to six questions on major chronic respiratory symptoms. This index was categorized as zero positive responses, one positive response, and two or more positive responses. Dependent variables included the occurrence of any respiratory illness, any upper respiratory illness, any lower respiratory illness, any wet cough lower respiratory illness, and any wheezing lower respiratory illness during the two-week block.

Initially, the incidence data were analyzed with conventional multiple logistic regression to identify patterns of effect, confounding, and effect modification. This method, however, assumes that the occurrence of an illness event

during any two-week block is independent of that in any other block. This assumption was violated by the data, which showed some interdependence of events. Consequently, the final analyses were performed using the generalized estimating equations described by Zeger and Liang (1986). This regression approach takes into account the correlation structure when estimating regression coefficients and their standard errors. Comparing the logistic and generalized estimating approaches showed that estimates of effect were comparable with the two methods, but that most standard errors were slightly larger with the generalized estimating equation approach.

The analyses using the generalized estimating equation approach were performed using a Statistical Analysis System (SAS) program (Karim and Zeger 1988). To apply this method, it is necessary to specify a link function, the mean-variance relation, and the structural form of the correlation matrix. For the incidence data, we used the logit link function and the binary mean-variance relation (variance = mean × [1 − mean]). The Poisson link function proved inappropriate for the data because the frequency distribution of occurrence of the illnesses in the two-week blocks had less dispersion than expected for a Poisson process. The choice of the structure of the correlation matrix was based on descriptive analyses of the correlations between the intervals separating repeated events in the same subjects. We found that the correlations remained fairly stable over the different ranges of the event numbers; based on this pattern of correlation, we selected the exchangeable correlation matrix. In exploratory analyses, we found that the results of the models were not dependent on the choice of correlation options.

Because interdependence was also found with the duration of illnesses, the generalized estimating equation approach was used for this outcome as well. For the duration data, we used the identity link function, the Gaussian mean-variance relation, and the exchangeable correlation matrix. To make the distributions more symmetrical, the durations were log transformed for analysis. The logarithm of the duration minus one day was used as the dependent variable. One day was subtracted from the duration because, by definition, symptoms had to last for two consecutive days to meet the criterion for an illness. The coefficients for the dichotomous independent variables estimate the mean difference between the logarithm of the duration minus one day for a specific exposure category, and the logarithm of the duration minus one day for the reference category. Therefore, the antilogarithm of the coefficient estimates the ratio of these two quantities.

All analyses were performed using the SAS data management and statistical analysis software (Statistical Analysis Institute 1990). The generalized estimating equations were applied using a SAS program supplied by Dr. Scott Zeger of Johns Hopkins University.

RESULTS

COHORT OBSERVATION

A total of 1,315 infants were enrolled. However, 110 completed 30 days or less of observation and were excluded from all subsequent analyses (Table 1). Of the remaining 1,205 subjects, 823 completed the full protocol, contributing 82.8% of the days at risk. Moving out of the study area and placement of the child in day care for more than 20 hours per week were the most frequent explanations for losses to observation. Little time at risk was contributed by subjects who declined to participate after enrollment or who were released because of noncompliance with study procedures. The overall distribution of time at risk by level of bedroom NO_2 concentration was skewed toward lower levels, with 22% of the total at concentrations above 20 ppb (Figure 1).

SUBJECT AND HOUSEHOLD CHARACTERISTICS

The stratified sampling achieved the target ratio of four homes with a gas stove for each home with an electric stove (Table 2). Subjects were compared with regard to demographic and household characteristics within strata defined by type of cooking stove in the residence at the time of en-

Table 1. Distribution of Days of Observation[a] for Subjects Followed for Thirty Days or Less, or for More Than Thirty Days, by Reason for Release

	30 Days or Less		More Than 30 Days	
	n	Days of Observation	*n*	Days of Observation
Mother smoking	2	23	7	1,217
Other smoking	8	77	11	1,240
Moved	7	66	128	35,278
Day care	24	162	109	23,491
Declined to participate	28	97	36	6,816
Noncompliant	25	114	52	14,261
Lost	1	0	25	7,019
Other	15	60	14	3,494
Completed protocol	—	—	823	445,537

[a] Days on which symptom and illness data were obtained and subjects were eligible for an illness event; see Methods section for criteria.

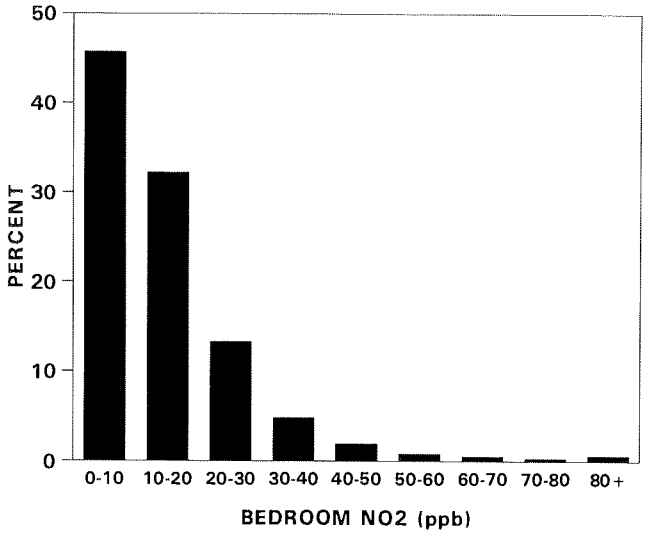


Figure 1. Distribution of time at risk by bedroom NO_2 concentration.

Table 2. Characteristics of Subjects and Subjects' Households by Type of Cooking Range[a]

Characteristic	Cooking Range	
	Gas (n = 952)	Electric (n = 253)
Gender		
Male	51.4	54.5
Female	48.6	45.5
Ethnicity/race		
Hispanic	39.9	30.8
Non-Hispanic white	51.9	65.6
Other	8.2	3.6
Maternal education		
⩽ 12 Years	39.1	22.1
13–15 Years	34.3	33.6
⩾ 16 Years	26.6	44.3
Household income[b]		
< $10,000	12.3	4.4
$10,000–$19,000	23.8	12.0
$20,000–$29,999	23.7	20.9
$30,000–$39,999	19.5	23.7
⩾ $40,000	20.7	39.0
Residence type		
Single family, unattached	72.1	81.0
Single family, attached	6.2	4.0
Multifamily	11.3	13.8
Mobile home	10.1	1.2
Area of living space[c]		
< 1,000 sq. feet	35.2	22.1
1,000–1,499 sq. feet	36.9	27.7
⩾ 1,500 sq. feet	27.9	50.2

[a] All values are expressed in percent.

[b] Not available for 23 homes with gas stoves and four with electric stoves.

[c] Not available for two homes with gas stoves.

rollment. Subjects from homes with gas stoves included a higher proportion of Hispanics; additionally, in comparison with the subjects from homes with electric stoves, the level of maternal education and the annual household income tended to be lower in homes with gas stoves. In addition, homes having gas stoves were less often single family and unattached homes, and were smaller on average.

The subjects from homes with gas and electric stoves were comparable for a number of other factors that affect the incidence of respiratory illnesses. Thus, 36.3% of subjects from gas stove homes were first-born children, in comparison with 34.8% from electric stove homes. The frequency of a parental history of asthma was also comparable in the two groups; 15.4% of subjects living in homes with gas stoves had at least one parent reporting positively compared with 15.8% in homes with electric stoves. The percentages were also comparable for a parental history of asthma or atopy: 48.0% versus 50.2%, respectively.

INCIDENCE RATES

During the study, there were 10,781 respiratory illness events of which 7,037 were classified as upper and 3,744 as lower; of the lower respiratory illnesses, 3,116 were accompanied by wet cough alone and 628 by wheezing. Cumulative frequency distributions for all respiratory illnesses, all upper respiratory illnesses, all lower respiratory illnesses, lower respiratory illnesses with wet cough, and lower respiratory illnesses with wheezing are provided in Figures 2 and 3 for the first year of life and for the first 18 months of life, respectively. Figure 2 covers the period up to the first birthday; on average, the first 30 days of life were not included. During the first year of life, most subjects had at least one

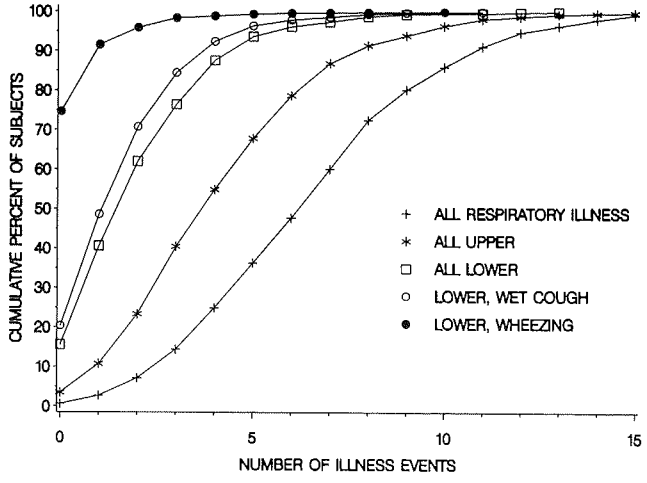


Figure 2. Cumulative percentage of subjects by numbers of each of the five types of respiratory illnesses from birth to 12 months of age.

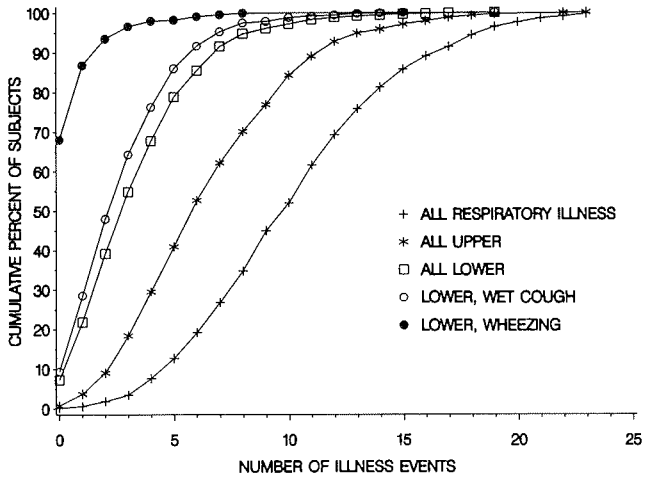


Figure 3. Cumulative percentage of subjects by numbers of each of the five types of respiratory illnesses from birth to 18 months of age.

upper and one lower respiratory tract illness (Figure 2). The median numbers of all respiratory illnesses, all upper respiratory illnesses, and all lower respiratory illnesses during the first 12 months of life were 7, 4, and 2, respectively. About 25% of subjects had a wheezing illness. The general patterns of the cumulative frequency distributions were comparable for the first 18 months of life (Figure 3).

Annualized incidence rates were calculated for the five types of respiratory illnesses (Table 3). These annualized rates were calculated with exclusion of days from the denominator during which the subjects were not at risk for illness, either because an illness was in progress or because the subject was away from his or her home and the diary was not maintained. The annualized rates are higher than the numbers of illnesses actually observed during a given age period (Figures 2 and 3) because of the exclusion of days not at risk. The rates are provided in strata corresponding to warmer months when illness rates and NO_2 levels are lower and colder months when illness rates and NO_2 levels are higher. As anticipated, the rates for all categories of illness were higher during the months of October through March than during April through September.

Consistent trends of increasing incidence rates of respiratory illness with increasing exposure to NO_2 were not evident for either the unlagged or lagged exposure variables (Table 3). Although apparent exposure-response relationships were present in a few strata, e.g., wheezing illnesses during October through March, exposure-response relationships were not uniformly evident. With further stratifi-

Table 3. Annualized Incidence Rates[a] for All Respiratory Illnesses by Season, Exposure to Nitrogen Dioxide, and Stove Type

	October–March		April–September	
Exposure Variable	Rate	95% CI	Rate	95% CI
All Respiratory Illnesses				
NO_2, 0–20 ppb	12.6	(12.3, 13.0)	6.8	(6.6, 7.1)
NO_2, 20–40 ppb	12.8	(12.1, 13.4)	7.8	(7.1, 8.4)
NO_2, > 40 ppb	11.8	(10.7, 13.0)	7.9	(6.1, 9.6)
NO_2, lagged 0–20 ppb	12.6	(12.3, 13.0)	6.9	(6.7, 7.1)
NO_2, lagged 20–40 ppb	13.0	(12.3, 13.7)	7.4	(6.8, 8.1)
NO_2, lagged > 40 ppb	11.2	(10.0, 12.5)	7.4	(5.7, 9.0)
Gas stove	12.6	(12.2, 12.9)	6.9	(6.7, 7.1)
Electric stove	12.7	(12.1, 13.4)	7.1	(6.7, 7.5)
All Upper Respiratory Illnesses				
NO_2, 0–20 ppb	7.7	(7.4, 8.0)	4.9	(4.7, 5.1)
NO_2, 20–40 ppb	7.9	(7.4, 8.4)	5.6	(5.1, 6.2)
NO_2, > 40 ppb	6.8	(5.9, 7.7)	6.1	(4.6, 7.7)
NO_2, lagged 0–20 ppb	7.7	(7.4, 8.0)	4.9	(4.8, 5.1)
NO_2, lagged 20–40 ppb	8.0	(7.5, 8.5)	5.3	(4.8, 5.9)
NO_2, lagged > 40 ppb	6.5	(5.5, 7.4)	5.8	(4.3, 7.2)
Gas stove	7.7	(7.4, 7.9)	5.0	(4.8, 5.2)
Electric stove	7.8	(7.3, 8.3)	4.9	(4.6, 5.2)

(Table continues next page.)

Table 3. (*continued*)

Exposure Variable	October–March Rate	October–March 95% CI	April–September Rate	April–September 95% CI
All Lower Respiratory Illnesses				
NO_2, 0–20 ppb	4.3	(4.1, 4.5)	1.8	(1.7, 1.9)
NO_2, 20–40 ppb	4.2	(3.9, 4.6)	1.9	(1.6, 2.3)
NO_2, > 40 ppb	4.5	(3.8, 5.2)	1.5	(0.8, 2.3)
NO_2, lagged 0–20 ppb	4.3	(4.1, 4.5)	1.8	(1.7, 1.9)
NO_2, lagged 20–40 ppb	4.3	(4.0, 4.7)	1.9	(1.6, 2.3)
NO_2, lagged > 40 ppb	4.3	(3.6, 5.0)	1.5	(0.8, 2.2)
Gas stove	4.3	(4.1, 4.5)	1.7	(1.6, 1.8)
Electric stove	4.3	(4.0, 4.7)	2.0	(1.8, 2.2)
Lower Respiratory Illnesses, Wet Cough				
NO_2, 0–20 ppb	3.6	(3.4, 3.8)	1.5	(1.4, 1.6)
NO_2, 20–40 ppb	3.5	(3.2, 3.8)	1.6	(1.4, 1.9)
NO_2, > 40 ppb	3.5	(2.9, 4.1)	1.0	(0.4, 1.6)
NO_2, lagged 0–20 ppb	3.6	(3.4, 3.7)	1.5	(1.4, 1.6)
NO_2, lagged 20–40 ppb	3.6	(3.2, 3.9)	1.6	(1.3, 1.9)
NO_2, lagged > 40 ppb	3.4	(2.7, 4.0)	1.3	(0.7, 2.0)
Gas stove	3.6	(3.4, 3.7)	1.4	(1.3, 1.5)
Electric stove	3.6	(3.2, 3.9)	1.7	(1.5, 1.9)
Lower Respiratory Illnesses, Wheezing				
NO_2, 0–20 ppb	0.6	(0.5, 0.7)	0.3	(0.2, 0.3)
NO_2, 20–40 ppb	0.7	(0.5, 0.8)	0.3	(0.2, 0.4)
NO_2, > 40 ppb	0.9	(0.6, 1.2)	0.5	(0.1, 0.9)
NO_2, lagged 0–20 ppb	0.6	(0.6, 0.7)	0.3	(0.2, 0.3)
NO_2, lagged 20–40 ppb	0.7	(0.5, 0.8)	0.3	(0.2, 0.5)
NO_2, lagged > 40 ppb	0.8	(0.5, 1.1)	0.2	(0.1, 0.4)
Gas stove	0.6	(0.6, 0.7)	0.3	(0.2, 0.3)
Electric stove	0.7	(0.5, 0.8)	0.3	(0.2, 0.3)

[a] In calculating incidence rates of respiratory illness, days at risk were those days of observation during which an illness was not in progress. Because subjects were at risk of illness following two symptom-free days, accrual of days at risk for illness began on the third day after enrollment. After an illness or after any period of seven days or more spent outside the home without health surveillance, counting of days at risk similarly began after two symptom-free days. These mandatory two-day intervals were not included in the days at risk. Incidence rates of the several types of illness were calculated as the ratio of the number of illness events to the number of days at risk, and annualized to 365 days at risk. By definition, days with a lower respiratory illness in progress were excluded from the days at risk for an upper respiratory illness. Confidence interval calculations are based on the Poisson distribution; confidence intervals do not take into account the interdependence of the illnesses and may be too narrow as a result.

cation by month, no relationship between unlagged NO_2 exposure and all lower respiratory illnesses was found (Figure 4). Illness rates were comparable for children living in homes with gas and electric stoves.

Illness rates were also examined within strata defined by unlagged exposures to NO_2 and potential confounding or modifying variables (Tables 4 and 5). Consistent trends suggesting exposure-response relationships between NO_2 concentrations and illness rates were not found. The findings were similar for the wet cough illnesses and wheezing illnesses that comprise the category of lower respiratory illness (Appendix A).

MULTIVARIATE MODELING OF INCIDENCE RATES

Initial multivariate analyses were performed using multiple logistic regression. This approach was used to screen for modification of the effect of NO_2 by other factors; the logistic models were run within strata of each potential modifying variable. The results of these models, which guided the selection of variables for the modeling using the generalized estimating equation method, are provided as Appendix B.

We then examined the effect of NO_2 exposure on illness incidence using the generalized estimating equation ap-

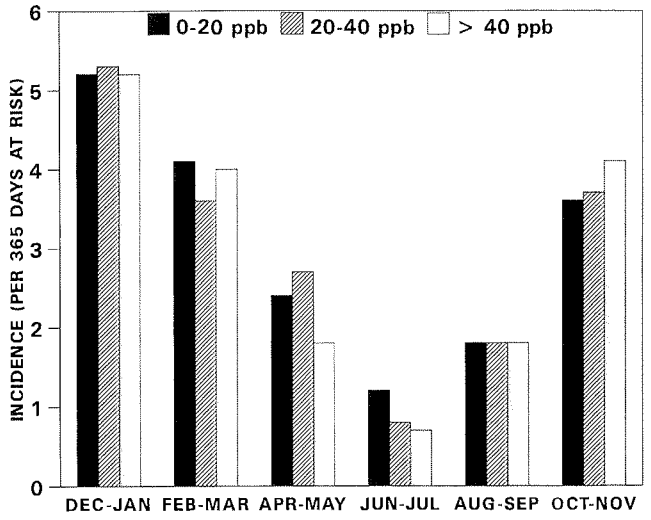


Figure 4. Annualized incidence rates for all lower respiratory illnesses by two-month intervals.

proach. These analyses assessed NO_2 exposure as a predictor of illness occurrence during two-week intervals; all models included indicator variables for potential confounding factors. The data set included 33,130 two-week intervals. For the analysis of unlagged NO_2, 3,558 blocks were excluded because of missing data for at least one of the variables included in the models. An additional 2,595 blocks were excluded from the analyses involving the lagged NO_2 because, by definition, exposure could not be estimated during the first four weeks of observation or until four weeks had lapsed after periods away from home.

The multivariate models examined the effect of the unlagged NO_2 exposures, lagged NO_2 exposures, and stove type (Table 6). None of the odds ratios was significantly different from unity, the value for the reference category of 0 through 20 ppb. Additionally, the odds ratios did not tend to increase consistently from the middle category of exposure to the highest category. Incidence rates were not increased in a comparison of time spent in homes with gas stoves with time in homes with electric stoves. The pattern of effect was similarly indicative of a lack of association within strata of variables considered as plausibly confounding or modifying the association of NO_2 with the incidence of all lower respiratory illnesses (Table 7). We also applied the generalized estimating equation approach to all strata showing statistically significant and positive associations of unlagged or lagged NO_2 exposure with illness incidence. Using the generalized estimation equation method, none of the increased odds ratios for these strata (unlagged NO_2 and all upper respiratory illnesses: maternal education of 16 or more years, non-Hispanic white, income $10,000 to $39,000; unlagged NO_2 and wet cough illnesses: Hispanic; lagged NO_2 and wet cough illnesses: maternal education of 16 or more years) remained statistically significant (data not shown).

We also added NO_2 exposure to the model as a continuous variable, while controlling for the same covariates included in Table 6. For each of the five illness variables, the estimated multiplier of the odds ratio per parts-per-billion increment of NO_2 was 0.999, with confidence limits extending from approximately 0.995 to 1.002.

By the age of 18 months, the completion of observation, 36 subjects had received a diagnosis of asthma from a physician, as documented by either maternal reports during the surveillance telephone calls or the questionnaire completed on leaving the study. The odds ratios for the effect of NO_2 on subjects who received a diagnosis of asthma tended to be increased, but confidence limits were wide because of the small number of subjects (Table 8). The odds ratios for lower respiratory illnesses with wet cough or wheezing in the asthmatic subjects were not higher for those living in homes with gas stoves than for those in electric stove homes: 1.18 (95% CI 0.39, 3.62) for wet cough illnesses and 0.84 (95% CI 0.31, 2.24) for wheezing illnesses. For the subjects without a diagnosis of asthma, the odds ratios for the effect of NO_2 changed little from the overall estimates (Tables 6 and 8).

MULTIVARIATE MODELING OF DURATION

Table 9 provides the medians and interquartile ranges for duration of the four types of illnesses by season; because of the substantial difference in duration between all upper and all lower respiratory illnesses, this information was not calculated for upper and lower respiratory illnesses combined. The duration of illness varied strongly with type of illness and to a small extent by season. Exposure to NO_2 and the durations of the four illness categories were not associated.

Multivariate modeling with the generalized estimating equations was then used to assess further the effect of NO_2 exposure on illness duration (Table 10). The model estimated the ratio of duration of illness minus one day in the exposure category to duration of illness minus one day in the reference category. For only one exposure and illness stratum, the highest category of lagged NO_2 exposure and wet cough, was this ratio significantly different from one. In this stratum, however, the ratio was less than one (odds ratio = 0.81; 95% CI 0.67, 0.97).

For illnesses with wheezing, the ratios were all above one, but none of the values was significantly different from one. Further analyses were directed at the stratum of exposures of greater than 40 ppb and wheezing illnesses. The analysis

Table 4. Annualized Incidence Rates[a] for All Respiratory Illnesses by Unlagged Nitrogen Dioxide Exposure and Selected Variables

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
April–September						
Atopy/asthma						
Parent history positive	7.3	(7.0, 7.6)	7.9	(6.9, 8.8)	8.4	(5.4, 11.3)
No parent history	6.4	(6.1, 6.7)	7.6	(6.7, 8.5)	7.5	(5.4, 9.7)
Breast feeding						
None	6.7	(6.4, 7.0)	7.8	(6.9, 8.6)	9.3	(6.7, 11.8)
Partial	7.6	(6.9, 8.3)	7.3	(5.6, 9.0)	5.7	(2.3, 9.0)
Full	6.8	(6.3, 7.2)	8.1	(6.6, 9.5)	6.7	(3.5, 9.9)
Day care						
0 Hours/week	5.9	(5.7, 6.2)	6.8	(6.0, 7.5)	7.1	(5.2, 9.0)
1–4 Hours/week	8.4	(7.8, 9.0)	9.3	(7.1, 11.4)	11.1	(3.4, 18.8)
⩾ 5 Hours/week	8.9	(8.4, 9.5)	10.2	(8.5, 11.8)	10.2	(5.3, 15.0)
Household income						
⩽ $10,000	7.5	(6.6, 8.4)	7.2	(5.8, 8.7)	7.5	(5.1, 9.9)
$10,000–$39,000	6.8	(6.5, 7.1)	7.8	(7.0, 8.6)	7.5	(4.9, 10.1)
⩾ $40,000	6.7	(6.3, 7.1)	8.0	(6.0, 10.0)	18.0	(4.7, 31.3)
Maternal education						
⩽ 12 Years	6.5	(6.2, 6.9)	7.2	(6.2, 8.2)	8.1	(5.1, 11.1)
13–15 Years	6.6	(6.2, 6.9)	7.4	(6.3, 8.5)	7.0	(4.2, 9.8)
⩾ 16 Years	7.4	(7.0, 7.8)	9.2	(7.8, 10.6)	8.5	(5.2, 11.8)
October–March						
Atopy/asthma						
Parent history positive	13.8	(13.3, 14.3)	13.2	(12.2, 14.2)	12.3	(10.5, 14.0)
No parent history	11.5	(11.0, 12.0)	12.5	(11.6, 13.3)	11.5	(9.9, 13.1)
Breast feeding						
None	12.4	(12.0, 12.9)	12.7	(11.9, 13.6)	12.4	(10.9, 14.0)
Partial	13.0	(12.0, 14.0)	13.4	(11.5, 15.2)	10.7	(7.6, 13.8)
Full	13.0	(12.2, 13.7)	12.6	(11.3, 14.0)	11.1	(8.8, 13.4)
Day care						
0 Hours/week	11.1	(10.7, 11.5)	11.8	(11.0, 12.6)	11.2	(9.9, 12.6)
1–4 Hours/week	16.3	(15.3, 17.4)	15.0	(13.1, 16.9)	12.5	(8.4, 16.5)
⩾ 5 Hours/week	14.9	(14.0, 15.8)	14.7	(13.1, 16.3)	14.1	(11.0, 17.2)
Household income						
⩽ $10,000	13.4	(11.8, 15.1)	10.7	(9.2, 12.3)	12.2	(10.0, 14.4)
$10,000–$39,000	12.4	(12.0, 12.9)	13.0	(12.2, 13.8)	10.9	(9.4, 12.4)
⩾ $40,000	13.0	(12.4, 13.7)	14.3	(12.3, 16.3)	19.1	(12.9, 25.3)
Maternal education						
⩽ 12 Years	11.4	(10.8, 12.0)	11.4	(10.4, 12.3)	12.5	(10.6, 14.4)
13–15 Years	12.6	(12.0, 13.2)	12.7	(11.6, 13.8)	11.5	(9.5, 13.5)
⩾ 16 Years	13.8	(13.2, 14.5)	15.2	(13.8, 16.7)	11.2	(8.9, 13.6)

[a] In calculating incidence rates of respiratory illness, days at risk were those days of observation during which an illness was not in progress. Because subjects were at risk of illness following two symptom-free days, accrual of days at risk for illness began on the third day after enrollment. After an illness or after any period of seven days or more spent outside the home without health surveillance, counting of days at risk similarly began after two symptom-free days. These mandatory two-day intervals were not included in the days at risk. Incidence rates of the several types of illness were calculated as the ratio of the number of illness events to the number of days at risk, and annualized to 365 days at risk. Confidence interval calculations are based on the Poisson distribution; confidence intervals do not take into account the interdependence of the illnesses and may be too narrow as a result.

Table 5. Annualized Incidence Rates[a] for All Lower Respiratory Illnesses by Unlagged Nitrogen Dioxide Exposure and Selected Variables

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
April–September						
Atopy/asthma						
Parent history positive	1.9	(1.8, 2.1)	2.1	(1.6, 2.5)	2.2	(0.8, 3.6)
No parent history	1.6	(1.5, 1.8)	1.8	(1.4, 2.2)	1.2	(0.4, 2.0)
Breast feeding						
None	1.9	(1.7, 2.0)	2.1	(1.7, 2.5)	2.1	(1.0, 3.3)
Partial	1.9	(1.6, 2.3)	1.5	(0.8, 2.3)	1.9	(0.0, 3.8)
Full	1.5	(1.3, 1.7)	1.9	(1.2, 2.5)	0.0	—
Day care						
0 Hours/week	1.5	(1.4, 1.7)	1.5	(1.2, 1.9)	1.3	(0.5, 2.1)
1–4 Hours/week	2.1	(1.8, 2.4)	2.7	(1.6, 3.8)	3.9	(0.5, 8.2)
⩾ 5 Hours/week	2.5	(2.2, 2.7)	2.8	(2.0, 3.7)	1.6	(0.2, 3.4)
Household income						
⩽ $10,000	2.1	(1.7, 2.6)	1.9	(1.2, 2.6)	2.4	(1.1, 3.7)
$10,000–$39,000	1.8	(1.7, 2.0)	2.0	(1.6, 2.4)	0.8	(0.0, 1.6)
⩾ $40,000	1.6	(1.4, 1.8)	1.9	(0.9, 2.8)	0.0	—
Maternal education						
⩽ 12 Years	1.7	(1.5, 1.9)	2.0	(1.5, 2.5)	2.6	(1.0, 4.2)
13–15 Years	1.8	(1.6, 2.0)	1.5	(1.0, 2.0)	1.1	(0.0, 2.1)
⩾ 16 Years	1.9	(1.7, 2.0)	2.5	(1.8, 3.2)	0.9	(0.1, 1.9)
October–March						
Atopy/asthma						
Parent history positive	4.6	(4.3, 4.9)	4.3	(3.8, 4.8)	4.8	(3.7, 5.8)
No parent history	4.0	(3.7, 4.2)	4.2	(3.7, 4.7)	4.3	(3.4, 5.2)
Breast feeding						
None	4.5	(4.2, 4.7)	4.5	(4.1, 5.0)	5.5	(4.5, 6.5)
Partial	4.3	(3.8, 4.9)	4.3	(3.3, 5.2)	3.9	(2.2, 5.7)
Full	3.8	(3.4, 4.1)	3.4	(2.8, 4.1)	2.6	(1.6, 3.6)
Day care						
0 Hours/week	3.8	(3.5, 4.0)	3.8	(3.4, 4.2)	4.4	(3.6, 5.2)
1–4 Hours/week	5.3	(4.7, 5.8)	4.8	(3.8, 5.8)	4.3	(2.0, 6.5)
⩾ 5 Hours/week	5.1	(4.6, 5.6)	5.5	(4.6, 6.4)	5.2	(3.4, 6.9)
Household income						
⩽ $10,000	5.5	(4.6, 6.5)	4.1	(3.2, 5.0)	5.3	(3.9, 6.6)
$10,000–$39,000	4.2	(3.9, 4.4)	4.3	(3.9, 4.7)	4.0	(3.1, 4.8)
⩾ $40,000	4.3	(4.0, 4.7)	4.5	(3.5, 5.5)	4.1	(1.6, 6.6)
Maternal education						
⩽ 12 Years	3.9	(3.6, 4.2)	4.0	(3.4, 4.5)	5.4	(4.2, 6.5)
13–15 Years	4.4	(4.1, 4.7)	4.0	(3.4, 4.5)	4.2	(3.0, 5.3)
⩾ 16 Years	4.5	(4.1, 4.8)	5.1	(4.3, 5.8)	3.5	(2.3, 4.8)

[a] In calculating incidence rates of respiratory illness, days at risk were those days of observation during which an illness was not in progress. Because subjects were at risk of illness following two symptom-free days, accrual of days at risk for illness began on the third day after enrollment. After an illness or after any period of seven days or more spent outside the home without health surveillance, counting of days at risk similarly began after two symptom-free days. These mandatory two-day intervals were not included in the days at risk. Incidence rates of the several types of illness were calculated as the ratio of the number of illness events to the number of days at risk, and annualized to 365 days at risk. Confidence interval calculations are based on the Poisson distribution; confidence intervals do not take into account the interdependence of the illnesses and may be too narrow as a result.

Table 6. Odds Ratios[a] for Effect of Nitrogen Dioxide Exposure on Incidence of Respiratory Illness

	All Illnesses		All Upper		All Lower		Lower, Wet Cough		Lower, Wheezing	
NO_2 Exposure	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Unlagged[b]										
20–40 ppb	1.04	(0.96, 1.12)	1.06	(0.97, 1.16)	0.98	(0.89, 1.09)	1.00	(0.89, 1.12)	0.92	(0.73, 1.15)
> 40 ppb	0.94	(0.81, 1.08)	0.95	(0.81, 1.11)	0.93	(0.76, 1.13)	0.94	(0.77, 1.16)	0.88	(0.56, 1.37)
Lagged[b]										
20–40 ppb	1.01	(0.93, 1.10)	1.06	(0.97, 1.16)	0.97	(0.87, 1.08)	0.97	(0.87, 1.09)	0.95	(0.75, 1.19)
> 40 ppb	0.92	(0.77, 1.10)	0.97	(0.81, 1.16)	0.91	(0.72, 1.15)	0.89	(0.68, 1.16)	0.98	(0.66, 1.48)
Gas Stove[c]	0.98	(0.90, 1.07)	1.04	(0.94, 1.14)	0.91	(0.81, 1.04)	0.94	(0.82, 1.07)	0.84	(0.64, 1.09)

[a] Obtained by generalized estimating equation method. Adjusted for season, age, gender, ethnicity, birth order, day care, income, maternal education, breast feeding, parental atopy and asthma, and maternal history of respiratory symptoms.

[b] Reference category is 0–20 ppb NO_2.

[c] Reference category is electric stove.

Table 7. Odds Ratios[a] Effects of Nitrogen Dioxide Exposure on Incidence of All Lower Respiratory Illnesses by Stratum of Nitrogen Dioxide Exposure and Selected Variables

	Sample Sizes		20–40 ppb NO_2[b]		> 40 ppb NO_2[b]	
	Children	Two-Week Intervals	Odds Ratio	95% CI	Odds Ratio	95% CI
Age						
0–6 Months	1,149	11,875	1.01	(0.86, 1.19)	0.95	(0.70, 1.28)
7–12 Months	983	9,913	0.85	(0.72, 1.01)	0.80	(0.57, 1.13)
13–18 Months	851	7,784	1.08	(0.89, 1.33)	1.05	(0.73, 1.52)
Household income						
< $10,000	120	2,721	0.88	(0.68, 1.14)	1.02	(0.72, 1.46)
$10,000–$39,000	746	19,202	1.03	(0.92, 1.16)	0.88	(0.69, 1.13)
⩾ $40,000	284	7,649	0.88	(0.65, 1.19)	0.98	(0.42, 2.27)
Season (6 months)						
October–March	1,103	13,995	0.99	(0.88, 1.12)	0.97	(0.77, 1.21)
April–September	1,102	15,577	1.07	(0.88, 1.31)	0.95	(0.57, 1.59)
Season (2 months)						
December–January	1,020	4,618	0.93	(0.77, 1.11)	0.85	(0.61, 1.17)
February–March	1,016	4,585	0.97	(0.79, 1.19)	0.85	(0.59, 1.24)
April–May	1,020	4,956	1.04	(0.79, 1.37)	0.75	(0.38, 1.45)
June–July	1,035	5,432	0.57	(0.32, 0.99)	0.54	(0.12, 2.41)
August–September	1,037	5,189	0.99	(0.69, 1.42)	1.08	(0.44, 2.64)
October–November	1,028	4,792	1.06	(0.87, 1.29)	1.11	(0.74, 1.66)
Maternal education						
⩽ 12 Years	398	9,823	0.94	(0.79, 1.11)	1.03	(0.75, 1.42)
13–15 Years	395	10,096	0.87	(0.74, 1.03)	0.91	(0.66, 1.24)
⩾ 16 Years	357	9,653	1.21	(1.00, 1.46)	0.76	(0.49, 1.17)
Parental atopy/asthma						
None	583	14,866	1.05	(0.91, 1.21)	0.94	(0.71, 1.24)
Atopy/no asthma	383	9,847	0.88	(0.73, 1.05)	1.03	(0.72, 1.46)
Asthma	184	4,859	1.02	(0.80, 1.30)	0.78	(0.51, 1.22)

[a] Obtained by generalized estimating equation method. Adjusted, as appropriate, for season, age, gender, ethnicity, birth order, day care, income, maternal education, breast feeding, parental atopy and asthma, and maternal history of respiratory symptoms.

[b] Reference category is 0–20 ppb NO_2.

Table 8. Odds Ratios[a] for Effects of Unlagged Nitrogen Dioxide Exposure on Illness Incidence by Physician Diagnosis of Asthma for the Subjects

	20–40 ppb NO_2[b]		> 40 ppb NO_2[b]	
Respiratory Illness Type	Odds Ratio	95% CI	Odds Ratio	95% CI
Subjects Without Asthma[c]				
All	1.03	(0.96, 1.12)	0.91	(0.79, 1.06)
All upper	1.06	(0.97, 1.15)	0.93	(0.29, 1.10)
All lower	0.98	(0.88, 1.08)	0.90	(0.73, 1.10)
Lower, wet cough	0.99	(0.88, 1.11)	0.94	(0.76, 1.16)
Lower, wheezing	0.89	(0.69, 1.16)	0.73	(0.45, 1.19)
Subjects With Asthma[c]				
All	1.35	(0.82, 2.21)	1.83	(0.81, 4.14)
All upper	1.26	(0.76, 2.10)	1.03	(0.34, 3.10)
All lower	1.14	(0.77, 1.69)	1.56	(0.56, 4.33)
Lower, wet cough	1.11	(0.64, 1.94)	0.98	(0.19, 5.16)
Lower, wheezing	1.20	(0.64, 2.26)	1.95	(0.90, 4.22)

[a] Obtained by generalized estimating equation method. Adjusted for season, age, gender, ethnicity, birth order, day care, income, maternal education, breast feeding, parental atopy and asthma, and maternal history of respiratory symptoms.

[b] Reference category is 0–20 ppb NO_2.

[c] Of 1,205 subjects, 36 had asthma and 1,169 did not.

Table 9. Median Duration of Respiratory Illnesses by Season and Nitrogen Dioxide Exposure[a]

	All Upper		All Lower		Lower, Wet Cough		Lower, Wheezing	
NO_2 Exposure	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
April–September								
Unlagged								
0–20 ppb	6	3–10	10	6–16	10	7–16	9	4–17
20–40 ppb	6	3–10	11	6–18	11	6–17	13	7–26
> 40 ppb	5	3–8	11	5–17	8	3–17	14	5–22
Lagged								
0–20 ppb	6	3–10	10	6–16	10	7–16	10	5–20
20–40 ppb	6	3–10	11	6–16	10	6–15	13	6–19
> 40 ppb	5	3–10	10	5–15	8	5–14	21	13–29
Gas stove	6	3–10	10	6–16	10	7–16	12	5–21
Electric stove	6	3–10	10	6–16	11	7–16	8	4–17
October–March								
Unlagged								
0–20 ppb	6	4–11	11	7–17	11	7–17	12	8–19
20–40 ppb	6	3–10	11	7–18	11	7–18	13	9–24
> 40 ppb	6	3–10	10	7–16	10	7–14	15	8–23
Lagged								
0–20 ppb	6	4–10	12	8–18	11	7–18	13	8–20
20–40 ppb	6	3–11	11	7–17	11	7–17	12	9–18
> 40 ppb	6	3–10	10	6–15	9	6–13	16	10–27
Gas stove	6	3–10	11	7–18	11	7–17	13	8–21
Electric stove	6	3–10	12	7–17	11	7–17	13	8–19

[a] All values are given in days.

Table 10. Effects of Nitrogen Dioxide Exposure on Duration of Respiratory Illness

NO_2 Exposure	All Upper		All lower		Lower, Wet Cough		Lower, Wheezing	
	Ratio[a]	95% CI	Ratio[a]	95% CI	Ratio[a]	95% CI	Ratio[a]	95% CI
Unlagged[b]								
20–40 ppb	1.00	(0.93, 1.07)	1.04	(0.96, 1.13)	1.01	(0.93, 1.11)	1.20	(0.97, 1.48)
> 40 ppb	0.97	(0.86, 1.10)	0.97	(0.82, 1.14)	0.89	(0.75, 1.07)	1.34	(0.93, 1.92)
Lagged[b]								
20–40 ppb	1.01	(0.95, 1.08)	0.97	(0.90, 1.06)	0.97	(0.89, 1.06)	1.06	(0.86, 1.31)
> 40 ppb	0.97	(0.85, 1.10)	0.89	(0.74, 1.07)	0.81[c]	(0.67, 0.97)[c]	1.41	(0.95, 2.09)
Gas stove[d]	0.98	(0.92, 1.05)	1.07	(0.99, 1.16)	1.06	(0.98, 1.15)	1.20	(0.99, 1.45)

[a] Ratio of duration minus unity in exposure category to duration minus unity in the reference category estimated by the generalized estimating equation approach. Model also includes indicator variables for season, age, gender, ethnicity, household income, maternal education, birth order, maternal history of respiratory symptoms, breast feeding, day care, and parental history of atopy or asthma.

[b] Reference category is 0–20 ppb NO_2.

[c] Significantly different from one.

[d] Reference category is electric stove.

was repeated with the exclusion of children with asthma; the resulting odds ratio was 1.36 (95% CI 0.87, 2.12). Comparison of the frequency distributions for illness duration by level of NO_2 showed that the tail of the distribution included a greater proportion of observations for the high exposure time; the proportions of illnesses of the shortest durations were comparable for the three exposure groups (Figure 5).

DISCUSSION

In a prospective cohort study extending from the first month of life to 18 months of age, we found that indoor exposure to NO_2 is associated with neither the incidence nor the duration of respiratory illnesses. The study was designed specifically to investigate the effects of NO_2 on the respiratory health of infants and toddlers (Samet et al. 1992). Subjects were selected with stratification by stove type to gain as much information as possible at the higher end of the distribution of indoor exposures. Potential confounding and effect modification by cigarette smoking were controlled by excluding subjects from households with smokers. By excluding subjects in day care for more than 20 hours per week, the study protocol reduced exposure misclassification from exposures during time spent away from home. Both NO_2 exposure and illness experience were intensively monitored. Data were collected on the many factors potentially associated with the incidence and duration of respiratory illnesses during early childhood (Graham 1990). Using multivariate techniques appropriate for longitudinal data (Zeger and Liang 1986), we controlled for these factors in examining the effects of NO_2 exposure on incidence and duration of respiratory illnesses. The study was designed to have sufficient power to detect effects of NO_2 exposure of magnitudes previously reported and in a range relevant to public health concern (Samet 1991; Samet et al. 1992).

Potential bias from misclassification of outcome and exposure and inadequate statistical power have limited the findings of previous studies of indoor NO_2 and the respiratory health of children (Vedal 1985; Samet and Utell 1990). However, these potential limitations cannot fully explain the lack of association of NO_2 exposure with either illness incidence or duration in our study.

Diagnosis of specific respiratory illnesses during the first years of life is difficult in both field and clinical settings.

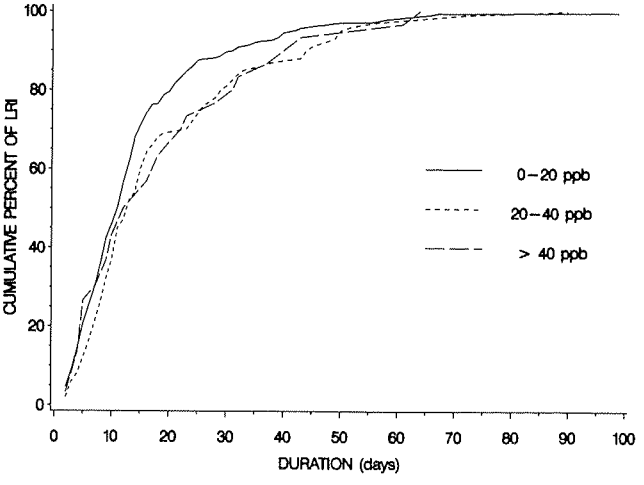


Figure 5. Cumulative frequency distributions of durations of lower respiratory illnesses in infants, without physician diagnosis of asthma. LRI = Lower respiratory illness.

Children of this age cannot communicate directly concerning symptoms, and the range of signs and symptoms is limited. Moreover, retrospective illness reports from parents are subject to information bias and are not sufficiently accurate for documenting complete illness histories (Graham 1990). Although distinct clinical syndromes of lower respiratory tract illness have been described, clinical criteria have not been established and validated in developed countries for classifying childhood respiratory illnesses as limited to the upper respiratory tract or involving the lower respiratory tract. Clinical information alone cannot link specific clinical patterns of illness to specific infectious organisms, except in the setting of epidemics with particular agents, e.g., bronchiolitis during an outbreak of respiratory syncytial virus infection. Thus, an accepted reference method for validating the surveillance approach used in this investigation is unavailable.

To limit bias from retrospective ascertainment of illnesses, we prospectively assessed illness incidence and duration using a surveillance approach based on the Tecumseh study of respiratory illnesses (Monto et al. 1971). Parents were kept unaware of the specific hypotheses of the study and were not provided with the results of the NO_2 measurements made in their homes until data collection was completed. The surveillance system was compared with conventional clinical methods by using data obtained by nurse practitioner assessment of ill and well subjects in their homes and by reviewing outpatient records (Samet et al. 1993). The validity of our methodology for illness identification was supported by the comparability of illness rates in this study with those previously reported for the Tecumseh study (Monto et al. 1971) and with findings from a study in Houston by Gardner and coworkers (1984). In the Tecumseh study, children under one year of age had an average of 6.1 respiratory illnesses annually, of which about two were classified as lower respiratory, based on productive cough, pain on respiration, or "wheezy breathing" (Monto et al. 1971). In the Houston Family Study, surveillance visits were made to the home every two weeks; the overall number of illnesses during the first year of life was about nine, of which an average of one was classified as involving the lower respiratory tract (Gardner et al. 1984). We also found the effects of season, birth order, and male gender on illness incidence to be similar to those anticipated from the Tecumseh study and others (Graham 1990; Samet et al. 1993).

In comparison with diagnoses made by our nurse practitioners and by the patients' own clinicians, the surveillance system was sensitive but nonspecific for detecting lower respiratory illnesses (Samet et al. 1993). Because there is no accepted reference standard for establishing the presence of infection at various levels of the respiratory tract, we used the clinician's diagnoses for comparison; the clinicians were not standardized and were likely to classify the more severely affected children as having a lower respiratory illness. The lack of specificity primarily reflected the classification of illnesses with wet cough as involving the lower respiratory tract. If NO_2 exposure increases the risk of specific clinical syndromes or respiratory pathogens involving the lower respiratory tract, the low specificity of the surveillance system could have been biased toward finding no association. However, the finding that NO_2 exposure and illness incidence and duration were not associated was consistent within the two types of lower respiratory illness: wet cough alone and wheezing. Furthermore, the toxicologic and epidemiologic evidence does not support such a focused hypothesis of lower respiratory tract involvement (Morrow 1984; Samet and Utell 1990; Samet 1991).

Exposure misclassification also cannot explain the lack of association. The measurement protocol was based on extensive pilot investigations of determinants of NO_2 exposure of infants (Harlos et al. 1987; Samet and Spengler 1989). In the pilot study, short-term personal exposures of infants meeting eligibility criteria were found to be associated tightly with bedroom concentrations. In data from the full study, we reaffirmed that bedroom concentration is a valid predictor of personal exposure to NO_2: personal exposure estimates based on time-weighted averages of measurements in the kitchen, activity room, and bedroom were closely comparable to personal exposure estimates based on bedroom measurements alone (see Part II, Lambert et al. 1993).

In animal studies, effects have been demonstrated using short-term exposures to concentrations of NO_2 one to two orders of magnitude higher than levels that occur in most homes (Morrow 1984). Therefore, exposures to short-term excursions to higher values during cooking may be more relevant for respiratory illness in infants than the two-week average exposures. Harlos (1988) has shown that cooking with a gas stove may generate short-term concentrations up to 200 to 400 ppb and transient peaks as high as 1,000 ppb. The information on time spent by our subjects in the kitchen during cooking shows that opportunities for exposure to these short-term peaks were infrequent for most subjects (Lambert et al. 1992). On 70% of the bimonthly calls, the subjects were reported to have spent no time in the kitchen while cooking was in progress during the previous 24 hours. When cooking was in progress, the median exposure time was only 20 minutes.

In interpreting our findings, consideration should also be given to the statistical power achieved by the study. The sample size calculations were based on anticipated rates of lower respiratory illness and physician-diagnosed lower respiratory illness, an outcome considered in several cross-

sectional studies of schoolchildren (Samet 1991). If a total of 720 infants completed 18 months of observation, we projected that the study would have adequate power for increments in the incidence rate as small as 20%, comparing the lowest stratum of exposure with the highest stratum (Samet et al. 1992). In fact, 1,315 infants were enrolled and 823 completed the full protocol (Table 1). Confidence intervals around effect estimates were relatively narrow, except for the wheezing illnesses, which accounted for only a small percentage of the total illnesses.

The initial power calculations, however, were based on the assumption of equal distribution of the days at risk across the strata of low, medium, and high NO_2 exposure. Less days at risk than anticipated were accrued in the higher exposure categories (Figure 1). We therefore recalculated the investigation's power using standard errors of the coefficients from the generalized estimating equation analysis and assuming that the coefficients are normally distributed (Table 11). Except for wheezing illnesses, these calculations indicated adequate power for detecting plausible levels of effect. For example, for all lower respiratory illnesses, 80% power was achieved at odds ratios of 1.15 and 1.33 for the middle and high strata of NO_2 exposure, respectively. Power was limited for lower respiratory illnesses with wheezing by the relatively small number of events. The levels of effects achieving 80% and 90% power were similar for duration.

A meta-analysis of studies of NO_2 exposure and respiratory illness estimates a 20% increment in risk per 15 ppb increment in long-term NO_2 exposure (Hasselblad et al. 1992). In our study, the median NO_2 levels for the three strata of exposure considered in the analysis were 8.7 ppb, 25.5 ppb, and 51.7 ppb. Using the exposure-response relationship from the meta-analysis, an increment of approximately 20% would be anticipated for the middle stratum of exposure, and approximately 60% would be anticipated for the high stratum. For effects of these magnitudes, power is adequate at the 90% level, except for wheezing illnesses (Table 11).

The health effects of NO_2 exposure indoors on children have been addressed in numerous epidemiologic studies of varying design (Samet et al. 1987; Samet 1991). In most of the studies, exposure was categorized by source descriptors alone, such as the type of cooking stove or water heater. However, a few recent studies have included some measurements of NO_2 (Dijkstra et al. 1990; Neas et al. 1991; Samet 1991; Braun-Fahrländer et al. 1992). A variety of health outcome measures have been considered in the studies of indoor NO_2, including respiratory infection, respiratory symptoms, and lung function level. The evidence from this heterogeneous group of investigations is not consistent in indicating adverse effects of NO_2 exposure (Samet et al. 1987; Samet 1991). Bias toward the null, resulting from misclassification of outcomes and exposures and inadequate sample sizes, probably affected many of these studies (Samet and Utell 1990).

Few studies have addressed the effects of NO_2 exposure on children during the first two years of life. In an early report from the Harvard Six Cities Study based on over 8,000 school children, Speizer and coworkers (1980) examined the cross-sectional association between current stove type and retrospective history of respiratory illness before the

Table 11. Effects of Nitrogen Dioxide Exposure Calculated to Have 80% and 90% Statistical Power for Illness Incidence and Duration by Stratum of Nitrogen Dioxide Exposure and Illness Type

	20–40 ppb NO_2[a]		> 40 ppb NO_2[a]	
Respiratory Illness Type	80% Power	90% Power	80% Power	90% Power
Illness Incidence[b]				
All	1.12	1.13	1.23	1.28
All upper	1.13	1.16	1.26	1.30
All lower	1.15	1.18	1.33	1.39
Lower, wet cough	1.17	1.20	1.35	1.41
Lower, wheezing	1.38	1.46	1.89	2.09
Illness Duration[c]				
All upper	1.10	1.12	1.19	1.23
All lower	1.12	1.14	1.26	1.31
Lower, wet cough	1.13	1.15	1.29	1.34
Lower, wheezing	1.36	1.42	1.67	1.82

[a] Reference category is 0–20 ppb NO_2.

[b] For illness incidence, the values shown are odds ratios.

[c] For illness duration, the values shown are ratios of geometric means for duration minus one day.

age of two years. Living in a home with a gas stove was associated with a 23% increase in risk. However, in a subsequent report based on an expansion of the population to over 10,000 children, this association was no longer statistically significant, although the magnitude of effect was comparable (Ware et al. 1984). In another population subsequently enrolled in the same six cities, stove type and history of doctor-diagnosed chest illness before age two were not associated (Dockery et al. 1987). Similar negative findings were reported for a large population of schoolchildren in western Pennsylvania (Schenker et al. 1983).

Only three other studies have prospectively examined NO_2 exposure and respiratory illnesses during the first year of life. Melia and associates (1983) assessed the occurrence of respiratory illnesses in relation to cooking stove type in a cohort of 390 infants. Illnesses were ascertained by a review of general practitioners' records and a retrospective history obtained from the mother when the child reached one year of age. In that study, the type of cooking stove was not associated with respiratory illnesses and symptoms. In a study conducted in Tayside in the United Kingdom, 1,565 infants were enrolled at birth and followed with periodic collection of information on respiratory illnesses at the time of routine home visits for well child health care; hospitalizations were also evaluated (Ogston et al. 1985). Stove type was not significantly associated with illness occurrence. In a more recent study, determinants of lower respiratory illness were assessed in 393 North Carolina children (Margolis et al. 1992). In that study, the parents were contacted every two weeks by telephone to ascertain symptoms of acute lower respiratory illness. In a report on that study, having a gas stove was not associated with a parent's report of persistent respiratory symptoms at age 12 months, as ascertained by questions on cough and wheezing. The investigators did not comment on type of cooking stove and illness incidence. None of these studies included measurements of NO_2.

Measurements of NO_2 in United Kingdom homes were made in several other studies conducted during the late 1970s and 1980s. Melia and colleagues (1982) measured NO_2 in a total of 337 homes in the same area in which the cross-sectional study showing an association between stove type and respiratory symptoms had been conducted (Melia et al. 1977). One-week measurements were made between January and March using passive diffusion tubes; the average level of NO_2 in the bedrooms of children living in homes with gas stoves was 30.1 ppb, compared with 13.7 ppb in the homes with electric stoves. In a study of a small number of inner-city residences in London, the mean NO_2 concentration in the bedrooms was only 24.1 ppb (Melia et al. 1990).

Our study in Albuquerque addressed the effect of indoor exposure to NO_2. In extending the findings to NO_2 in outdoor air, consideration should be given to differences in the chemical species of nitrogen oxides in indoor and outdoor environments. Combustion processes generate a mixture of nitric oxide and NO_2, but much of the nitric oxide is converted to NO_2. The formation of nitrous acid in indoor environments also has been demonstrated (Pitts et al. 1985; Brauer et al. 1991); measurements made in 10 homes included in the Albuquerque study confirmed this phenomenon (Spengler et al. 1993). Because of the large amount of time spent indoors at home, the dose of hydrogen ion received from nitrous acid may have health significance. In outdoor air, NO_2 is derived from vehicle emissions and fossil fuel combustion, mostly for industrial purposes and the generation of electric power. The NO_2 is typically present in a complex mixture with other components that may also have adverse respiratory effects: respirable particles, sulfur oxides, and photochemical oxidants. With prolonged residence in the atmosphere, nitrogen oxides may be transformed to acidic nitrate species that may adversely affect the respiratory tract through their acidity (Spengler et al. 1990). Thus, the adverse effects of NO_2 in indoor and outdoor environments may be mediated through comparable toxicologic mechanisms: injury by oxidant and acid species. However, the complex mixtures of pollutants present in indoor and outdoor air are clearly distinct under most circumstances.

The findings of this study can be extended with confidence to most homes with gas stoves in the many regions of the United States where the outdoor air is not heavily polluted by NO_2. Concentrations in the Albuquerque homes were comparable to those measured in homes in Portage, WI, Kingston-Harriman, TN, and Minneapolis-St. Paul, MN (Spengler et al. 1983; Drye et al. 1989; Neas et al. 1991; Dr. Marian Marbury, personal communication). Higher concentrations have been reported in small apartments in Harlem, NY (Goldstein et al. 1987) and public housing in Chattanooga, TN (Parkhurst et al. 1989). However, given the extent of information available on NO_2 concentrations in homes with gas stoves, it is unlikely that typical concentrations in single family residences in other U.S. locations differ substantially from the measurements made in Albuquerque.

As evidence on NO_2 is evaluated and synthesized for the purposes of risk assessment and standard setting, we suggest that this study of NO_2 and respiratory illnesses in Albuquerque children merits emphasis. The study was designed and implemented specifically to address NO_2, and the resulting data have provided a precise characterization of risk that does not appear to have been significantly af-

fected by bias. Recently, meta-analysis has been used to summarize the epidemiologic evidence on NO_2 (Hasselblad et al. 1992); this meta-analysis is also incorporated into the draft criteria document for NO_2 (U.S. Environmental Protection Agency 1992). Although meta-analysis represents an appropriate technique for summarizing evidence, this approach may lead to a potentially misleading summary estimate unless the individual studies are weighted by a measure of quality as well as a measure of information quantity.

Our study shows that living in a home with a gas stove does not adversely affect the respiratory health of children during the first 18 months of life. This age group was targeted because of the high rates of respiratory illness, possible heightened susceptibility of the developing lung to injury, and earlier reports indicating adverse effects of NO_2 in this age range (Speizer 1980). Although the study did not show an adverse effect of NO_2 on respiratory illness incidence and duration, it addressed only one of the hypothesized outcomes of NO_2 exposure. These other effects include exacerbation of asthma and chronic obstructive pulmonary disease, increased respiratory symptoms, and reduced lung function. The study also did not include children with low birth weight, significant congenital defects, or chronic respiratory conditions other than asthma, or children exposed to parental smoking. While other adverse effects of NO_2 need further investigation in populations, we caution that any new studies of the effects of NO_2 during the first years of life be directed at children with increased susceptibility because of intrinsic lung disease or healthy children having higher exposures than in our study.

ACKNOWLEDGMENTS

We would like to thank the parents, children, and physicians of Albuquerque whose conscientious efforts made this study possible. We are also grateful for the many contributions of the other members of the team: Kay Browning, Diane Corry, Genevieve Degani, Robert DeVivo, Pamela England, Stella Falter, Lee Fernando, Dawn Hamilton, David Harlos, Louise Kahn, Veronica Ketchbaw, Val King, Anna Kratochvil, Teri Law, Dona Lewis, Beth Meysenberg, Bella Montgomery, Emilie O'Mara, Beth Owens, Delinda Scenters, Jenny Su, Anna Reade, and Lauri Wast. We are also grateful for the invaluable advice of Drs. Caroline Hall, George Ray, Ira Tager, and Lynn Taussig, who participated in discussions about the design of the study. We also would like to acknowledge the guidance of the HEI Research Committee, and particularly the thoughtful suggestions of Dr. John Tukey.

REFERENCES

Brauer M, Koutrakis P, Keeler GJ, Spengler JD. 1991. Indoor and outdoor concentrations of inorganic acidic aerosols and gases. J Air Waste Manage Assoc 41:171–181.

Braun-Fahrländer C, Ackermann-Liebrich U, Schwartz J, Gnehm HP, Rutishauser M, Wanner HU. 1992. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis 145:42–47.

Breslow NE, Day NE. 1987. Statistical Methods in Cancer Research, Vol. II, The Design and Analysis of Cohort Studies. IARC publication No. 82. International Agency for Research on Cancer, Lyon, France.

Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JSM. 1990. Respiratory health effects of the indoor environment in a population of Dutch children. Am Rev Respir Dis 142:1172–1178.

Dockery DW, Spengler JD, Speizer FE, Ferris Jr BG, Ware JH, Brunekreef B. 1987. Associations of health status with indicators of indoor air pollution from an epidemiologic study in six U.S. cities. In: Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Vol. 2, Environmental Tobacco Smoke, Multicomponent Studies, Radon, Sick Buildings, Odours and Irritants, Hyperactivities and Allergies (Seifert B, Esdorn H, Fischer M, Ruden H, eds.) pp. 203–207. Institute for Water, Soil, and Air Hygiene, Berlin, Germany.

Drye EE, Ozkaynak H, Burbank B, Billick IH, Spengler JD, Ryan PB, Baker PE, Colome SD. 1989. Development of models for predicting the distribution of indoor nitrogen dioxide concentrations. J Air Pollut Control Assoc 39:1169–1177.

Ferris BG. 1978. Epidemiology standardization project. Am Rev Respir Dis 118:1–120.

Gardner G, Frank AL, Taber LH. 1984. Effects of social and family factors on viral respiratory infection and illness in the first year of life. J Epidemiol Community Health 38: 42–48.

Goldstein IF, Andrews LR, Lieber K, Foutrakis G, Kazembe F, Huang P, Hayes C. 1987. Acute exposure to nitrogen dioxide and pulmonary function. In: Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Vol. 1, Vol. 1, Volatile Organic Compounds, Combustion Gases, Particles and Fibres, Microbiological Agents (Seifert B, Esdorn H, Fischer M, Rüden H, Wegner

J, eds.) pp. 293–297. Institute for Water, Soil, and Air Hygiene, Berlin, Germany.

Graham NMH. 1990. The epidemiology of acute respiratory infections in children and adults: A global perspective. Epidemiol Rev 12:149–178.

Harlos DP. 1988. Acute Exposure to Nitrogen Dioxide During Cooking or Commuting (doctoral dissertation). Harvard School of Public Health, Boston, MA.

Harlos DP, Marbury M, Samet J, Spengler JD. 1987. Relating indoor NO_2 levels to infant personal exposures. Atmos Environ 21:369–378.

Hasselblad V, Eddy DM, Kotchmar DJ. 1992. Synthesis of environmental evidence: Nitrogen dioxide epidemiology studies. J Air Waste Manage Assoc 42:662–671.

Lambert WE, Samet JM, Hunt WC, Skipper BJ, Schwab M, Spengler JD. 1993. Nitrogen Dioxide and Respiratory Illness in Children: Part II, Assessment of Exposure to Nitrogen Dioxide. Research Report Number 58. Health Effects Institute, Cambridge, MA.

Marbury MC, Harlos DP, Samet JM, Spengler JD. 1988. Indoor residential NO_2 concentrations in Albuquerque, NM. J Air Pollut Control Assoc 38:392–398.

Margolis PA, Greenburg RA, Keyes LL, LaVange LM, Chapman RS, Denny FW, Bauman KE, Boat BW. 1992. Lower respiratory illness in infants and low socioeconomic status. Am J Public Health 82:1119–1126.

Melia RJW, Chinn S, Rona RJ. 1990. Indoor levels of NO_2 associated with gas cookers and kerosene heaters in inner city areas of England. Atmos Environ 24:177–180.

Melia RJW, Florey C du V, Altman DG, Swan AV. 1977. Association between gas cooking and respiratory disease in children. Br Med J 2:149–152.

Melia RJW, Florey C du V, Morris RW, Goldstein BD, John THH, Clark D, Craighead IB, Mackinlay JC. 1982. Childhood respiratory illness and the home environment: II. Association between respiratory illness and nitrogen dioxide, temperature, and relative humidity. Int J Epidemiol 11:164–169.

Melia RJ, Florey C du V, Sittampalam Y, Watkins C. 1983. The relation between respiratory illness in infants and gas cooking in the US: A preliminary report. In: Proceedings of the 6th World Congress in Air Quality, August 16–20, 1983. International Union of Air Pollution Prevention Associations, Paris, France.

Monto AS, Napier JA, Metzner HL. 1971. The Tecumseh study of respiratory illness: I. Plan of study and observations on syndromes of acute respiratory disease. Am J Epidemiol 94:269–279.

Morrow PE. 1984. Toxicological data on NO_2: An overview. J Toxicol Environ Health 13:205–227.

National Research Council, Subcommittee on Nitrous Oxides, Committee on Medical and Biological Effects of Environmental Pollutants. 1976. Nitrogen Oxides. National Academy Press, Washington, DC.

Neas LM, Dockery DW, Ware JH, Spengler JD, Speizer FE, Ferris BG Jr. 1991. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. Am J Epidemiol 134:204–219.

Ogston SA, Florey C du V, Walker CHM. 1985. The Tayside infant morbidity and mortality study: Effect on health of using gas for cooking. Br Med J 290:957–960.

Palmes ED, Gunnison AS, Dimaggio J, Tomczyk C. 1976. Personal sampler for nitrogen dioxide. Am Ind Hyg Assoc J 37:570–577.

Parkhurst WJ, Dumyahn T, Cropp JW. 1989. Intervention study to reduce nitrogen dioxide in a Chattanooga, Tennessee, public housing development. In: Combustion Processes and the Quality of the Indoor Environment (Harper JP, ed.) pp. 74–84. Air and Waste Management Association, Pittsburgh, PA.

Pennington JE. 1988. Effects of automotive emissions on susceptibility to respiratory infections. In: Air Pollution, the Automobile, and Public Health (Watson AY, Bates RR, Kennedy D, eds.) pp. 499–518. National Academy Press, Washington, D.C.

Pitts JN, Wallington TJ, Biermann HW, Winer AM. 1985. Identification and measurement of nitrous acid in an indoor environment. Atmos Environ 19:763.

Samet JM. 1991. Nitrogen dioxide. In: Indoor Air Pollution: A Health Perspective (Samet JM, Spengler JD, eds.) pp. 170–186. Johns Hopkins University Press, Baltimore, MD.

Samet JM, Cushing AH, Lambert WE, Hunt WC, McLaren LC, Young SA, Skipper BJ. 1993. Comparability of parent-reported respiratory illnesses to clinical diagnoses. Am Rev Respir Dis (in press).

Samet JM, Lambert WE, Skipper BJ, Cushing AH, McLaren LC, Schwab M, Spengler JD. 1992. A study of respiratory illnesses in infants and NO_2 exposure. Arch Environ Health 47:57–63.

Samet JM, Marbury MC, Spengler JD. 1987. Health effects and sources of indoor air pollution, Part I. Am Rev Respir Dis 136:1486–1508.

Samet JM, Spengler JD. 1989. Nitrogen Dioxide and Respiratory Infections: Pilot Investigations. Research Report Number 28. Health Effects Institute, Cambridge, MA.

Samet JM, Utell MJ. 1990. The risk of nitrogen dioxide: What have we learned from epidemiological and clinical studies? Toxicol Ind Health 6:247–262.

Schenker MB, Samet JM, Speizer FE. 1983. Risk factors for childhood respiratory disease: The effect of host factors and home environmental exposures. Am Rev Respir Dis 128: 1038–1043.

Speizer FE, Ferris B Jr, Bishop YM, Spengler JD. 1980. Respiratory disease rates and pulmonary function in children associated with NO_2 exposure. Am Rev Respir Dis 121:3–10.

Spengler JD, Brauer M, Koutrakis P. 1990. Acid air and health. Environ Sci Technol 24:946–956.

Spengler J, Brauer M, Samet J, Lambert W. 1993. Nitrous acid in Albuquerque homes. Environ Sci Technol (in press).

Spengler JD, Duffy CP, Letz R, Tibbitts TW, Ferris BG Jr. 1983. Nitrogen dioxide inside and outside 137 homes and implications for ambient air quality standards and health effects research. Environ Sci Technol 17:164–168.

Statistical Analysis Institute. 1990. SAS Language: Reference, Version 6, 1st ed. SAS Institute, Cary, NC.

U.S. Department of Health and Human Services. 1986. The Health Consequences of Involuntary Smoking: A report of the Surgeon General. Office of Smoking and Health, DHHS, Rockville, MD.

Vedal S. 1985. Epidemiological studies of childhood illness and pulmonary function associated with gas stove use. In: Indoor Air and Human Health (Gammage RB, ed.) pp. 303–316. Lewis Publishers, Chelsea, MI.

Ware JH, Dockery DW, Spiro A III, Speizer FE, Ferris BG Jr. 1984. Passive smoking, gas cooking, and respiratory health in children living in six cities. Am Rev Respir Dis 129:366–374.

Zeger SL, Liang K-Y. 1986. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42:121–130.

APPENDIX A. Rates of Respiratory Illness by Level of Nitrogen Dioxide Exposure and Selected Factors

Table A.1. Annualized Incidence Rates[a] of All Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, October–March

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	13.8	(13.3, 14.3)	13.2	(12.2, 14.2)	12.3	(10.5, 14.0)
No parent history	11.5	(11.0, 12.0)	12.5	(11.6, 13.3)	11.5	(9.9, 13.1)
Breast feeding						
None	12.4	(12.0, 12.9)	12.7	(11.9, 13.6)	12.4	(10.9, 14.0)
Partial	13.0	(12.0, 14.0)	13.4	(11.5, 15.2)	10.7	(7.6, 13.8)
Full	13.0	(12.2, 13.7)	12.6	(11.3, 14.0)	11.1	(8.8, 13.4)
Day care						
0 Hours/week	11.1	(10.7, 11.5)	11.8	(11.0, 12.6)	11.2	(9.9, 12.6)
1–4 Hours/week	16.3	(15.3, 17.4)	15.0	(13.1, 16.9)	12.5	(8.4, 16.5)
⩾ 5 Hours/week	14.9	(14.0, 15.8)	14.7	(13.1, 16.3)	14.1	(11.0, 17.2)
Household income						
⩽ $10,000	13.4	(11.8, 15.1)	10.7	(9.2, 12.3)	12.2	(10.0, 14.4)
$10,000–$39,000	12.4	(12.0, 12.9)	13.0	(12.2, 13.8)	10.9	(9.4, 12.4)
⩾ $40,000	13.0	(12.4, 13.7)	14.3	(12.3, 16.3)	19.1	(12.9, 25.3)
Maternal education						
⩽ 12 Years	11.4	(10.8, 12.0)	11.4	(10.4, 12.3)	12.5	(10.6, 14.4)
13–15 Years	12.6	(12.0, 13.2)	12.7	(11.6, 13.8)	11.5	(9.5, 13.5)
⩾ 16 Years	13.8	(13.2, 14.5)	15.2	(13.8, 16.7)	11.2	(8.9, 13.6)

[a] In calculating incidence rates of respiratory illness, days at risk were those days of observation during which an illness was not in progress. Because subjects were at risk of illness following two symptom-free days, accrual of days at risk for illness began on the third day after enrollment. After an illness or after any period of seven days or more spent outside the home without health surveillance, counting of days at risk similarly began after two symptom-free days. These mandatory two-day intervals were not included in the days at risk. Incidence rates of the several types of illness were calculated as the ratio of the number of illness events to the number of days at risk, and annualized to 365 days at risk. Confidence interval calculations are based on the Poisson distribution; confidence intervals do not take into account the interdependence of the illnesses and may be too narrow as a result.

Table A.2. Annualized Incidence Rates[a] of All Upper Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, October–March

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	8.4	(8.0, 8.9)	8.2	(7.5, 9.0)	6.9	(5.6, 8.2)
No parent history	7.0	(6.6, 7.4)	7.6	(6.9, 8.3)	6.6	(5.4, 7.9)
Breast feeding						
None	7.3	(6.9, 7.6)	7.5	(6.9, 8.2)	6.4	(5.3, 7.5)
Partial	8.0	(7.2, 8.8)	8.3	(6.9, 9.8)	6.3	(3.9, 8.7)
Full	8.6	(8.0, 9.2)	8.6	(7.5, 9.8)	8.0	(6.1, 10.0)
Day care						
0 Hours/week	6.8	(6.5, 7.2)	7.5	(6.9, 8.1)	6.4	(5.3, 7.4)
1–4 Hours/week	10.0	(9.2, 10.8)	9.3	(7.8, 10.9)	7.7	(4.6, 10.9)
⩾ 5 Hours/week	8.9	(8.2, 9.5)	8.3	(7.1, 9.5)	8.0	(5.7, 10.4)
Household income						
⩽ $10,000	7.1	(6.0, 8.3)	6.1	(5.0, 7.3)	6.5	(4.9, 8.1)
$10,000–$39,000	7.6	(7.2, 8.0)	8.0	(7.4, 8.7)	6.4	(5.3, 7.6)
⩾ $40,000	8.0	(7.5, 8.5)	9.0	(7.5, 10.6)	13.8	(8.5, 19.1)
Maternal education						
⩽ 12 Years	6.9	(6.5, 7.4)	6.8	(6.1, 7.6)	6.5	(5.2, 7.9)
13–15 Years	7.5	(7.1, 8.0)	8.1	(7.2, 9.0)	6.8	(5.2, 8.3)
⩾ 16 Years	8.6	(8.1, 9.1)	9.3	(8.1, 10.4)	7.2	(5.3, 9.1)

[a] See footnote to Table A.1. By definition, days with a lower respiratory illness in progress were excluded from the days at risk for an upper respiratory illness.

Table A.3. Annualized Incidence Rates[a] of All Lower Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, October–March

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	4.6	(4.3, 4.9)	4.3	(3.8, 4.8)	4.8	(3.7, 5.8)
No parent history	4.0	(3.7, 4.2)	4.2	(3.7, 4.7)	4.3	(3.4, 5.2)
Breast feeding						
None	4.5	(4.2, 4.7)	4.5	(4.1, 5.0)	5.5	(4.5, 6.5)
Partial	4.3	(3.8, 4.9)	4.3	(3.3, 5.2)	3.9	(2.2, 5.7)
Full	3.8	(3.4, 4.1)	3.4	(2.8, 4.1)	2.6	(1.6, 3.6)
Day care						
0 Hours/week	3.8	(3.5, 4.0)	3.8	(3.4, 4.2)	4.4	(3.6, 5.2)
1–4 Hours/week	5.3	(4.7, 5.8)	4.8	(3.8, 5.8)	4.3	(2.0, 6.5)
⩾ 5 Hours/week	5.1	(4.6, 5.6)	5.5	(4.6, 6.4)	5.2	(3.4, 6.9)
Household income						
⩽ $10,000	5.5	(4.6, 6.5)	4.1	(3.2, 5.0)	5.3	(3.9, 6.6)
$10,000–$39,000	4.2	(3.9, 4.4)	4.3	(3.9, 4.7)	4.0	(3.1, 4.8)
⩾ $40,000	4.3	(4.0, 4.7)	4.5	(3.5, 5.5)	4.1	(1.6, 6.6)
Maternal education						
⩽ 12 Years	3.9	(3.6, 4.2)	4.0	(3.4, 4.5)	5.4	(4.2, 6.5)
13–15 Years	4.4	(4.1, 4.7)	4.0	(3.4, 4.5)	4.2	(3.0, 5.3)
⩾ 16 Years	4.5	(4.1, 4.8)	5.1	(4.3, 5.8)	3.5	(2.3, 4.8)

[a] See footnote to Table A.1.

Table A.4. Annualized Incidence Rates[a] of Lower Respiratory Illness, Wet Cough, by Unlagged Nitrogen Dioxide Exposure and Selected Variables, October–March

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	3.7	(3.4, 4.0)	3.4	(2.9, 3.8)	3.9	(3.0, 4.9)
No parent history	3.4	(3.2, 3.7)	3.6	(3.1, 4.0)	3.2	(2.4, 4.0)
Breast feeding						
None	3.8	(3.6, 4.1)	3.7	(3.3, 4.1)	4.2	(3.4, 5.1)
Partial	3.4	(3.0, 3.9)	3.4	(2.5, 4.2)	3.5	(1.8, 5.2)
Full	3.0	(2.7, 3.3)	2.9	(2.3, 3.6)	2.0	(1.1, 2.9)
Day care						
0 Hours/week	3.1	(2.9, 3.3)	3.2	(2.8, 3.5)	3.3	(2.6, 4.0)
1–4 Hours/week	4.6	(4.1, 5.1)	4.1	(3.2, 5.0)	4.0	(1.8, 6.1)
⩾ 5 Hours/week	4.2	(3.8, 4.6)	4.2	(3.4, 5.0)	4.3	(2.7, 5.8)
Household income						
⩽ $10,000	4.0	(3.2, 4.8)	3.3	(2.5, 4.2)	3.5	(2.4, 4.6)
$10,000–$39,000	3.5	(3.3, 3.7)	3.5	(3.1, 3.9)	3.4	(2.6, 4.2)
⩾ $40,000	3.8	(3.4, 4.1)	4.0	(3.1, 5.0)	2.9	(0.7, 5.0)
Maternal education						
⩽ 12 Years	3.2	(2.9, 3.5)	3.1	(2.7, 3.6)	4.0	(3.0, 5.0)
13–15 Years	3.7	(3.4, 4.0)	3.3	(2.8, 3.8)	3.5	(2.5, 4.6)
⩾ 16 Years	3.8	(3.5, 4.1)	4.3	(3.6, 5.0)	2.7	(1.6, 3.8)

[a] See footnote to Table A.1.

Table A.5. Annualized Incidence Rates[a] of Lower Respiratory Illness, Wheezing, by Unlagged Nitrogen Dioxide Exposure and Selected Variables, October–March

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	0.8	(0.7, 0.9)	0.8	(0.6, 1.0)	0.8	(0.4, 1.2)
No parent history	0.5	(0.4, 0.6)	0.5	(0.4, 0.7)	1.0	(0.6, 1.4)
Breast feeding						
None	0.6	(0.5, 0.6)	0.7	(0.6, 0.9)	1.1	(0.7, 1.5)
Partial	0.8	(0.6, 1.0)	0.8	(0.4, 1.2)	0.4	(0.1, 0.9)
Full	0.7	(0.5, 0.8)	0.4	(0.2, 0.7)	0.6	(0.1, 1.0)
Day care						
0 Hours/week	0.6	(0.5, 0.7)	0.6	(0.4, 0.7)	1.0	(0.6, 1.3)
1–4 Hours/week	0.6	(0.4, 0.8)	0.6	(0.3, 0.9)	0.3	(0.3, 0.8)
⩾ 5 Hours/week	0.8	(0.6, 1.0)	1.1	(0.7, 1.5)	0.8	(0.2, 1.4)
Household income						
⩽ $10,000	1.4	(0.9, 1.8)	0.7	(0.4, 1.1)	1.6	(0.9, 2.3)
$10,000-$39,000	0.6	(0.5, 0.7)	0.7	(0.5, 0.9)	0.5	(0.2, 0.8)
⩾ $40,000	0.5	(0.4, 0.6)	0.4	(0.1, 0.7)	1.1	(0.1, 2.4)
Maternal education						
⩽ 12 Years	0.6	(0.5, 0.8)	0.7	(0.5, 1.0)	1.2	(0.7, 1.7)
13–15 Years	0.6	(0.5, 0.7)	0.6	(0.4, 0.8)	0.6	(0.2, 1.0)
⩾ 16 Years	0.6	(0.5, 0.7)	0.7	(0.4, 0.9)	0.7	(0.2, 1.3)

[a] See footnote to Table A.1.

Table A.6. Annualized Incidence Rates[a] of All Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, April–September

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	7.3	(7.0, 7.6)	7.9	(6.9, 8.8)	8.4	(5.4, 11.3)
No parent history	6.4	(6.1, 6.7)	7.6	(6.7, 8.5)	7.5	(5.4, 9.7)
Breast feeding						
None	6.7	(6.4, 7.0)	7.8	(6.9, 8.6)	9.3	(6.7, 11.8)
Partial	7.6	(6.9, 8.3)	7.3	(5.6, 9.0)	5.7	(2.3, 9.0)
Full	6.8	(6.3, 7.2)	8.1	(6.6, 9.5)	6.7	(3.5, 9.9)
Day care						
0 Hours/week	5.9	(5.7, 6.2)	6.8	(6.0, 7.5)	7.1	(5.2, 9.0)
1–4 Hours/week	8.4	(7.8, 9.0)	9.3	(7.1, 11.4)	11.1	(3.4, 18.8)
⩾ 5 Hours/week	8.9	(8.4, 9.5)	10.2	(8.5, 11.8)	10.2	(5.3, 15.0)
Household income						
⩽ $10,000	7.5	(6.6, 8.4)	7.2	(5.8, 8.7)	7.5	(5.1, 9.9)
$10,000–$39,000	6.8	(6.5, 7.1)	7.8	(7.0, 8.6)	7.5	(4.9, 10.1)
⩾ $40,000	6.7	(6.3, 7.1)	8.0	(6.0, 10.0)	18.0	(4.7, 31.3)
Maternal education						
⩽ 12 Years	6.5	(6.2, 6.9)	7.2	(6.2, 8.2)	8.1	(5.1, 11.1)
13–15 Years	6.6	(6.2, 6.9)	7.4	(6.3, 8.5)	7.0	(4.2, 9.8)
⩾ 16 Years	7.4	(7.0, 7.8)	9.2	(7.8, 10.6)	8.5	(5.2, 11.8)

[a] See footnote to Table A.1.

Table A.7. Annualized Incidence Rates[a] of All Upper Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, April–September

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	5.2	(4.9, 5.5)	5.6	(4.8, 6.4)	5.9	(3.5, 8.4)
No parent history	4.6	(4.3, 4.8)	5.7	(4.9, 6.4)	6.3	(4.3, 8.2)
Breast feeding						
None	4.7	(4.5, 4.9)	5.5	(4.8, 6.2)	6.9	(4.7, 9.1)
Partial	5.5	(4.9, 6.0)	5.6	(4.1, 7.1)	3.6	(0.9, 6.3)
Full	5.2	(4.8, 5.5)	6.1	(4.8, 7.3)	6.7	(3.5, 9.9)
Day care						
0 Hours/week	4.3	(4.1, 4.5)	5.1	(4.5, 5.8)	5.6	(3.9, 7.3)
1–4 Hours/week	6.1	(5.6, 6.6)	6.3	(4.4, 8.1)	6.9	(0.9, 13.0)
⩾ 5 Hours/week	6.2	(5.7, 6.7)	7.0	(5.6, 8.3)	8.4	(4.0, 12.8)
Household income						
⩽ $10,000	5.2	(4.5, 5.9)	5.2	(3.9, 6.5)	5.0	(3.0, 6.9)
$10,000–$39,000	4.8	(4.6, 5.0)	5.6	(4.9, 6.3)	6.5	(4.1, 9.0)
⩾ $40,000	5.0	(4.6, 5.3)	6.0	(4.2, 7.7)	18.0	(4.7, 31.3)
Maternal education						
⩽ 12 Years	4.7	(4.4, 5.0)	5.0	(4.2, 5.9)	5.2	(2.8, 7.6)
13–15 Years	4.6	(4.3, 4.9)	5.7	(4.7, 6.7)	5.9	(3.3, 8.4)
⩾ 16 Years	5.4	(5.0, 5.7)	6.4	(5.2, 7.6)	7.5	(4.5, 10.6)

[a] See footnote to Table A.1. By definition, days with a lower respiratory illness in progress were excluded from the days at risk for an upper respiratory illness.

Table A.8. Annualized Incidence Rates[a] of All Lower Respiratory Illness by Unlagged Nitrogen Dioxide Exposure and Selected Variables, April–September

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	1.9	(1.8, 2.1)	2.1	(1.6, 2.5)	2.2	(0.8, 3.6)
No parent history	1.6	(1.5, 1.8)	1.8	(1.4, 2.2)	1.2	(0.4, 2.0)
Breast feeding						
None	1.9	(1.7, 2.0)	2.1	(1.7, 2.5)	2.1	(1.0, 3.3)
Partial	1.9	(1.6, 2.3)	1.5	(0.8, 2.3)	1.9	(0.0, 3.8)
Full	1.5	(1.3, 1.7)	1.9	(1.2, 2.5)	0.0	(0.0, 0.0)
Day care						
0 Hours/week	1.5	(1.4, 1.7)	1.5	(1.2, 1.9)	1.3	(0.5, 2.1)
1–4 Hours/week	2.1	(1.8, 2.4)	2.7	(1.6, 3.8)	3.9	(0.5, 8.2)
⩾ 5 Hours/week	2.5	(2.2, 2.7)	2.8	(2.0, 3.7)	1.6	(0.2, 3.4)
Household income						
⩽ $10,000	2.1	(1.7, 2.6)	1.9	(1.2, 2.6)	2.4	(1.1, 3.7)
$10,000–$39,000	1.8	(1.7, 2.0)	2.0	(1.6, 2.4)	0.8	(0.0, 1.6)
⩾ $40,000	1.6	(1.4, 1.8)	1.9	(0.9, 2.8)	0.0	(0.0, 0.0)
Maternal education						
⩽ 12 Years	1.7	(1.5, 1.9)	2.0	(1.5, 2.5)	2.6	(1.0, 4.2)
13–15 Years	1.8	(1.6, 2.0)	1.5	(1.0, 2.0)	1.1	(0.0, 2.1)
⩾ 16 Years	1.9	(1.7, 2.0)	2.5	(1.8, 3.2)	0.9	(0.1, 1.9)

[a] See footnote to Table A.1.

Table A.9. Annualized Incidence Rates[a] of Lower Respiratory Illness, Wet Cough, by Unlagged Nitrogen Dioxide Exposure and Selected Variables, April–September

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	1.6	(1.4, 1.7)	1.8	(1.3, 2.2)	1.5	(0.3, 2.6)
No parent history	1.4	(1.3, 1.6)	1.5	(1.1, 1.9)	0.7	(0.1, 1.4)
Breast feeding						
None	1.6	(1.4, 1.7)	1.8	(1.4, 2.2)	1.7	(0.6, 2.7)
Partial	1.7	(1.4, 2.0)	1.1	(0.5, 1.7)	0.5	(0.5, 1.4)
Full	1.2	(1.0, 1.4)	1.6	(1.0, 2.2)	0.0	(0.0, 0.0)
Day care						
0 Hours/week	1.3	(1.2, 1.4)	1.3	(1.0, 1.6)	1.0	(0.3, 1.6)
1–4 Hours/week	1.8	(1.5, 2.0)	2.4	(1.4, 3.5)	0.0	(0.0, 0.0)
⩾ 5 Hours/week	2.1	(1.8, 2.4)	2.4	(1.6, 3.2)	1.6	(0.2, 3.4)
Household income						
⩽ $10,000	1.6	(1.2, 2.0)	1.3	(0.7, 1.9)	1.3	(0.3, 2.2)
$10,000–$39,000	1.5	(1.4, 1.7)	1.8	(1.4, 2.1)	0.8	(0.0, 1.6)
⩾ $40,000	1.4	(1.2, 1.6)	1.6	(0.7, 2.5)	0.0	(0.0, 0.0)
Maternal education						
⩽ 12 Years	1.4	(1.2, 1.5)	1.6	(1.1, 2.0)	1.8	(0.5, 3.2)
13–15 Years	1.5	(1.3, 1.7)	1.4	(1.0, 1.9)	0.8	(0.1, 1.7)
⩾ 16 Years	1.6	(1.4, 1.8)	2.1	(1.5, 2.7)	0.3	(0.3, 0.9)

[a] See footnote to Table A.1.

Table A.10. Annualized Incidence Rates[a] of Lower Respiratory Illness, Wheezing, by Unlagged Nitrogen Dioxide Exposure and Selected Variables, April–September

	0–20 ppb NO_2		20–40 ppb NO_2		> 40 ppb NO_2	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Atopy/asthma						
Parent history positive	0.3	(0.3, 0.4)	0.3	(0.1, 0.4)	0.7	(0.1, 1.5)
No parent history	0.2	(0.2, 0.3)	0.3	(0.1, 0.5)	0.4	(0.1, 0.9)
Breast feeding						
None	0.3	(0.2, 0.3)	0.3	(0.1, 0.4)	0.5	(0.1, 1.0)
Partial	0.3	(0.1, 0.4)	0.4	(0.1, 0.8)	1.4	(0.2, 3.0)
Full	0.2	(0.2, 0.3)	0.2	(0.0, 0.5)	0.0	(0.0, 0.0)
Day care						
0 Hours/week	0.3	(0.2, 0.3)	0.2	(0.1, 0.4)	0.4	(0.0, 0.8)
1–4 Hours/week	0.3	(0.2, 0.4)	0.2	(0.1, 0.5)	3.7	(0.5, 7.9)
⩾ 5 Hours/week	0.3	(0.2, 0.4)	0.4	(0.1, 0.7)	0.0	(0.0, 0.0)
Household income						
⩽ $10,000	0.5	(0.3, 0.7)	0.6	(0.2, 0.9)	1.1	(0.2, 2.0)
$10,000–$39,000	0.3	(0.2, 0.3)	0.2	(0.1, 0.3)	0.0	(0.0, 0.0)
⩾ $40,000	0.2	(0.1, 0.3)	0.2	(0.1, 0.6)	0.0	(0.0, 0.0)
Maternal education						
⩽ 12 Years	0.3	(0.2, 0.4)	0.4	(0.2, 0.6)	0.7	(0.1, 1.6)
13–15 Years	0.2	(0.2, 0.3)	0.1	(0.0, 0.2)	0.3	(0.2, 0.8)
⩾ 16 Years	0.2	(0.2, 0.3)	0.4	(0.1, 0.7)	0.6	(0.2, 1.4)

[a] See footnote to Table A.1.

APPENDIX B. Odds Ratios from Logistic Regressions for Effect of Nitrogen Dioxide Exposure on Incidence

Table B.1. Odds Ratios for Effects of Nitrogen Dioxide Exposure Variables on Incidence of All Respiratory Illness, Overall and Stratified by Various Factors[a]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas Stove Homes[b]	20–40 ppb	> 40 ppb	20–40 ppb	> 40 ppb
Overall	1.00	1.04	0.93	1.02	0.93
Age					
0–6 Months	0.96	1.10	1.05	1.08	1.03
7–12 Months	1.03	0.98	0.84	0.91	0.86
13–18 Months	1.01	1.04	0.84	1.09	0.86
Atopy/asthma					
Parent history positive	1.12[d]	1.15[d]	0.97	1.12[d]	1.08
No parent history	0.91[d]	0.95	0.91	0.93	0.81[d]
Ethnicity					
Hispanic	1.08	1.03	1.13	1.03	1.15
Non-Hispanic	0.98	1.07	0.80[d]	1.02	0.79[d]
Household income					
⩽ $10,000	1.01	0.91	0.96	0.86	1.00
$10,000–$39,000	0.99	1.08	0.90	1.06	0.89
⩾ $40,000	1.09	1.07	1.64[d]	1.04	1.49
Maternal education					
⩽ 12 Years	1.11	1.01	1.11	0.97	1.20
13–15 Years	0.94	0.96	0.87	0.96	0.91
⩾ 16 Years	1.02	1.26[d]	0.91	1.22[d]	0.74[d]
Season					
Fall/winter	1.03	1.07	0.93	1.07	0.96
Spring/summer	0.96	1.07	1.16	0.99	1.00

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

[c] Compared with 0–20 ppb NO_2.

[d] Odds ratio differs significantly from 1.0, $p < 0.05$.

Table B.2. Odds Ratios for Effects of Nitrogen Dioxide Exposure Variables on Incidence of All Upper Respiratory Illness, Overall and Stratified by Various Factors[a]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas Stove Homes[b]	20–40 ppb	> 40 ppb	20–40 ppb	> 40 ppb
Overall	1.04	1.08	0.96	1.07	0.99
Age					
0–6 Months	1.00	1.13[d]	1.07	1.10	1.08
7–12 Months	1.11	1.09	0.90	1.02	0.97
13–18 Months	1.01	0.98	0.85	1.09	0.84
Atopy/asthma					
Parent history positive	1.21[d]	1.19[d]	0.98	1.16[d]	1.06
No parent history	0.91[d]	0.97	0.95	0.98	0.92
Ethnicity					
Hispanic	1.08	1.04	0.96	1.03	1.04
Non-Hispanic	1.03	1.10[d]	1.00	1.10	0.97
Household income					
⩽ $10,000	0.90	0.98	0.94	0.99	1.07
$10,000–$39,000	1.07	1.09[d]	0.97	1.09	0.95
⩾ $40,000	1.04	1.14	1.59	1.10	1.79[d]
Maternal education					
⩽ 12 Years	1.11	1.02	0.96	1.03	0.98
13–15 Years	1.03	1.06	0.93	1.05	1.09
⩾ 16 Years	1.03	1.19[d]	1.11	1.16[d]	0.93
Season					
Fall/winter	1.05	1.08	0.90	1.09	0.95
Spring/summer	1.02	1.11	1.30	1.04	1.13

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

[c] Compared with 0–20 ppb NO_2.

[d] Odds ratio differs significantly from 1.0, $p < 0.05$.

Table B.3. Odds Ratios for Effects of Nitrogen Dioxide Exposure Variables on Incidence of All Lower Respiratory Illness, Overall and Stratified by Various Factors[a]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas Stove Homes[b]	20–40 ppb	> 40 ppb	20–40 ppb	> 40 ppb
Overall	0.95	0.97	0.91	0.96	0.89
Age					
0–6 Months	0.92	1.01	0.97	1.06	0.96
7–12 Months	0.94	0.85[d]	0.79	0.83[d]	0.78
13–18 Months	0.99	1.08	0.95	1.02	0.96
Atopy/asthma					
Parent history positive	0.96	1.02	0.94	1.01	1.08
No parent history	0.96	0.93	0.89	0.93	0.76
Ethnicity					
Hispanic	1.06	0.97	1.25	1.02	1.25
Non-Hispanic	0.92	0.98	0.63[d]	0.93	0.65[d]
Household income					
⩽ $10,000	1.23	0.83	0.96	0.77	0.91
$10,000–$39,000	0.89[d]	1.02	0.87	1.00	0.89
⩾ $40,000	1.12	0.92	1.18	0.97	0.78
Maternal education					
⩽ 12 Years	1.05	0.96	1.24	0.89	1.41[d]
13–15 Years	0.86[d]	0.84[d]	0.83	0.89	0.73
⩾ 16 Years	1.00	1.21[d]	0.69	1.22[d]	0.62[d]
Season					
Fall/winter	1.00	1.01	0.99	1.03	1.00
Spring/summer	0.86[d]	0.99	0.78	0.90	0.75

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

[c] Compared with 0–20 ppb NO_2.

[d] Odds ratio differs significantly from 1.0, $p < 0.05$.

Table B.4. Odds Ratios for Effects of Nitrogen Dioxide Exposure Variables on Incidence of Lower Respiratory Illness, Wet Cough, Overall and Stratified by Various Factors[a]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas Stove Homes[b]	20–40 ppb	> 40 ppb	20–40 ppb	> 40 ppb
Overall	0.97	1.00	0.92	0.97	0.88
Age					
0–6 Months	1.00	1.11	1.14	1.13	1.08
7–12 Months	0.93	0.86	0.73	0.86	0.67[d]
13–18 Months	0.98	1.03	0.92	0.95	0.97
Atopy/asthma					
Parent history positive	1.01	1.01	0.86	1.01	0.99
No parent history	0.94	0.99	1.00	0.95	0.79
Ethnicity					
Hispanic	1.04	1.00	1.33[d]	1.00	1.25
Non-Hispanic	0.95	1.00	0.62[d]	0.96	0.62[d]
Household income					
⩽ $10,000	1.49	0.83	0.99	0.80	0.88
$10,000–$39,000	0.90	1.04	0.92	1.01	0.94
⩾ $40,000	1.11	0.99	0.96	1.01	0.62
Maternal education					
⩽ 12 Years	1.11	0.96	1.19	0.86	1.33
13–15 Years	0.90	0.91	0.93	0.94	0.83
⩾ 16 Years	0.98	1.20	0.68	1.22[d]	0.51[d]
Season					
Fall/winter	1.04	1.03	1.00	1.04	0.97
Spring/summer	0.85[d]	1.04	0.86	0.94	0.78

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

[c] Compared with 0–20 ppb NO_2.

[d] Odds ratio differs significantly from 1.0, $p < 0.05$.

Table B.5. Odds Ratios for Effects of Nitrogen Dioxide Exposure Variables on Incidence of Lower Respiratory Illness, Wheezing, Overall and Stratified by Various Factors[a]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas Stove Homes[b]	20–40 ppb	> 40 ppb	20–40 ppb	> 40 ppb
Overall	0.87	0.89	0.87	0.92	0.98
Age					
0–6 Months	0.70[d]	0.78	0.60	0.85	0.67
7–12 Months	0.96	0.80	1.12	0.70	1.42
13–18 Months	1.08	1.31	1.11	1.45	0.93
Atopy/asthma					
Parent history positive	0.71[d]	1.09	1.38	1.01	1.51
No parent history	1.04	0.79	0.64	0.88	0.71
Ethnicity					
Hispanic	1.10	0.91	0.99	1.10	1.23
Non-Hispanic	0.81	0.90	0.76	0.83	0.83
Household income					
⩽ $10,000	0.81	0.90	0.96	0.76	1.09
$10,000–$39,000	0.84	0.94	0.68	0.99	0.68
⩾ $40,000	1.14	0.50	2.40	0.64	1.93
Maternal education					
⩽ 12 Years	0.81	1.01	1.36	1.10	1.61
13–15 Years	0.75	0.57[d]	0.47	0.68	0.40
⩾ 16 Years	1.06	1.26	0.83	1.14	1.23
Season					
Fall/winter	0.85	0.94	0.99	1.00	1.12
Spring/summer	0.94	0.81	0.50	0.73	0.64

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

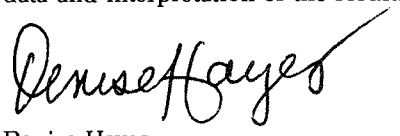
[c] Compared with 0–20 ppb NO_2.

[d] Odds ratio differs significantly from 1.0, $p < 0.05$.

APPENDIX C. External Quality Assurance Report

The conduct of this study has been subjected to periodic audits by the Quality Assurance Team from Arthur D. Little, Inc. The audits have included in-process monitoring of study activities and audits of the data. The dates of audits, nature of the visit, and quality assurance personnel participating in the audits are listed in Table C.1. The results of the inspections were reported to the Director of Research of the Health Effects Institute, who was responsible for transmitting the reports to the Principal Investigator.

Observations made during these visits indicate that the study is well documented and that the report describes the methods and standard operating procedures used. Review of the final report indicates that deviations from the protocol and standard operating procedures have been considered and addressed, as appropriate, in the analysis of the data and interpretation of the results of the study.



Denise Hayes
Quality Assurance Officer
Arthur D. Little

Table C.1. Audits by Arthur D. Little Quality Assurance Team

Date	Participating Personnel	Location[a]	Focus of Audit Review
12/18/87	K. Menzies	Internal	NO_2 analysis protocol and standard operating procedures
1/21/88	D. Hayes F. Cadigan Jr. M.G. Ott	UNM	Health and exposure assessment standard operating procedures
1/21/88	K. Menzies	HSPH	Palmes tubes production and shipment procedures, laboratory analysis, data reduction
4/26–27/88	D. Hayes	UNM	Study procedures, data reporting
7/19/88	D. Hayes K. Menzies	HSPH	Analytical procedures, data reporting
8/9–10/88	D. Hayes	UNM	Home visit procedures, data reporting
12/12–13/88	D. Hayes	UNM	Health and exposure assessment procedures, data reporting
1/5/89	K. Menzies	HSPH	Analytical procedures, data reporting
7/25/89	K. Menzies	HSPH	Analytical procedures, data reporting
9/7–8/89	D. Hayes	UNM	Data audit
1/5/90	R. O'Neil	HSPH	NO_2 monitor instrument calibration procedures
4/25–5/14/90	R. O'Neil	HSPH	Analytical procedures, data reporting
5/30–31/90	D. Hayes R. O'Neil	UNM	Peak exposure monitoring, QA home visit, data handling, QA procedures
3/22–23/91	R. O'Neil C. Lamontagne	HSPH	Data calculations, documentation procedures

[a] UNM = University of New Mexico; HSPH = Harvard School of Public Health.

ABOUT THE AUTHORS

Jonathan M. Samet, M.D., the Principal Investigator for these studies, is Professor of Medicine and Chief of the Pulmonary and Critical Care Division at the University of New Mexico Hospital, and is the Director of Epidemiology at the New Mexico Tumor Registry. He received his M.D. degree from the University of Rochester School of Medicine and Dentistry, and received clinical training in internal medicine and the subspecialty of pulmonary diseases. He completed a three-year fellowship in clinical epidemiology at the Channing Laboratory, Harvard Medical School, and has an M.S. in epidemiology from the Harvard School of Public Health. His research interests focus on environmental and occupational epidemiology and the effects of chemical and radioactive agents on the lung.

William E. Lambert, the Project Coordinator for these studies, is Research Assistant Professor in the Department of Family and Community Medicine. He is completing his Ph.D. at the University of California, Irvine, in the Department of Environmental Health and Design, School of Social Ecology. His research interests have focused on assessment of exposure to air pollutants and the measurement of health effects in the community setting.

Betty J. Skipper, Ph.D., the Project Biostatistician, has also been affiliated with the Study since the earliest stages of its inception and design. She is Professor of Family and Community Medicine at the University of New Mexico School of Medicine. She received her Ph.D. degree in biostatistics from Case Western Reserve University.

Alice H. Cushing, M.D., the Project Pediatrician, has been affiliated with the University of New Mexico Study of Infant Respiratory Illness since its inception in 1983. She is a Professor of Pediatrics at the University of New Mexico School of Medicine and her research has focused on the epidemiology of infectious diseases, including diarrheal and respiratory diseases. She received her M.D. from the University of Colorado.

William C. Hunt, M.A., is a statistician and programmer with the New Mexico Tumor Registry. He received his M.A. from the Department of Mathematics and Statistics at the University of New Mexico.

Stephen A. Young, Ph.D., is a Research Associate in the Department of Microbiology at the University of New Mexico School of Medicine. He received his Ph.D. in Medical Sciences at University of New Mexico and completed postdoctoral training in laboratory medicine at the University of Washington. He is the current Director of the Clinical Virology Laboratory. His research interests include viral pathogenesis and rapid diagnostic methods.

Leroy C. McLaren, Ph.D., designed the system used in this study for isolation of viruses, and was Director of the Clinical Virology Laboratory from 1964 to 1990. Before retirement in 1990, he was Professor of Microbiology at the University of New Mexico School of Medicine. He received M.A. and Ph.D. degrees from the University of California, Los Angeles.

Margo Schwab, Ph.D., coordinated the handling of the NO_2 data at the Harvard School of Public Health. This work included developing the quality control program, and the statistical analyses of household and seasonal factors determining NO_2 concentrations in homes. She received her Ph.D. degree in Geography from Clark University. Her research interests include human exposure assessment and time-activity patterns of populations. She is currently with ManTech Environmental, Inc., Research Triangle Park, NC.

Jack Spengler, Ph.D., the Principal Investigator for the Harvard component of the study, is Professor of Environmental Health Sciences at the Harvard School of Public Health. He received a Ph.D. in Atmospheric Sciences from the State University of New York at Albany, and an M.S. in Environmental Health Sciences from the Harvard School of Public Health. His research has focused on the measurement of air pollutants inside homes and on the assessment of personal exposure to air pollutants.

PUBLICATIONS RESULTING FROM THIS RESEARCH

The following list includes only those papers that have been submitted for publication at the time this report went to press. Please call or write to the Health Effects Institute for an updated list.

Samet JM, Utell MJ. 1990. The risk of nitrogen dioxide: What have we learned from epidemiological and clinical studies? Toxicol Ind Health 6:247–262.

Samet JM, Lambert WE. 1991. Epidemiologic approaches for assessing health risks from complex mixtures in indoor air. Environ Health Perspect 95:71–74.

Samet JM, Utell MJ. 1991. The environment and the lung: Changing perspectives. JAMA 226:670–675.

Lambert WE, Samet JM, Dockery DW. 1992. Community air pollution. In: Environmental and Occupational Health, 2nd Ed. (Rom WN, ed.) Little, Brown & Co., Boston, MA.

Lambert WE, Samet JM, Stidley CA, Spengler JD. 1992. Classification of exposure to residential nitrogen dioxide exposure. Atmos Environ 26A:2185–2192.

Samet JM, Lambert WE, Skipper BJ, Cushing AH, McLaren LC, Schwab M, Spengler JD. 1992. A study of respiratory illnesses in infants and nitrogen dioxide exposure. Arch Environ Health 47:57–63.

Spengler JD, Brauer M, Samet JM, Lambert WE. 1993. Nitrous acid in Albuquerque, New Mexico, homes. Environ Sci Technol (in press).

ABBREVIATIONS

CI	confidence interval
NAAQS	National Ambient Air Quality Standard
NO_2	nitrogen dioxide
ppb	parts per billion

NOTE REGARDING REVIEW OF THIS DOCUMENT

This study was supported by funds from the U.S. Environmental Protection Agency, the motor vehicle industry, and the Gas Research Institute. Although this document was produced with partial funding by the EPA under assistance agreement 816285 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 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.

Nitrogen Dioxide and Respiratory Illness in Children

Part II: Assessment of Exposure to Nitrogen Dioxide

William E. Lambert, Jonathan M. Samet, William C. Hunt, Betty J. Skipper, Margo Schwab, and John D. Spengler

ABSTRACT

Repeated measurements of nitrogen dioxide were obtained from 1988 to 1991 in the homes of 1,205 infants living in Albuquerque, NM. Passive diffusion samplers were used to obtain a series of two-week integrated measurements from the home of each infant for use in a cohort study of the relation of residential exposure to nitrogen dioxide and respiratory illnesses.

Information on stove use and time spent inside the residence was collected at two-week and two-month intervals, respectively. During the winter, in the bedrooms of homes with gas cooking stoves, mean nitrogen dioxide concentrations were 21 parts per billion (ppb)*; mean concentrations in the living room and kitchen were 29 ppb and 34 ppb, respectively. In homes with electric cooking stoves, the mean bedroom concentration was 7 ppb during the winter. Lower indoor concentrations were observed during the summer in homes with both gas and electric stoves. On average, infants spent approximately 12.3 hours per day in their bedrooms, 7.3 hours in the living rooms, 35 minutes in the kitchens, and 3.8 hours out of their homes. (As a condition of participation, none of the infants spent more than 20 hours per week in day care outside of their homes.) The mean time infants spent in the kitchen during cooking was approximately nine minutes per day. We tested whether exposures of infants living in homes with gas stoves could be reasonably estimated by measurements in the bedroom in comparison with time-weighted average concentrations based on time-activity data and simultaneous nitrogen dioxide measurements in the kitchen, living room, and bedroom. In 1,937 two-week intervals from 587 infants, 90% of time-weighted exposure (on the three-level classification used in this study) estimates were in agreement with estimates based on bedroom concentrations alone. The agreement of the time-weighted nitrogen dioxide exposure estimates with the bedroom concentrations is attributed to limited amounts of cooking stove use (the mean was 29 minutes per day), small room-to-room differences in nitrogen dioxide concentrations (the mean kitchen-bedroom difference was 12 ppb), and the relatively large proportion of time that infants spent in their bedrooms.

INTRODUCTION

In most areas of the United States, combustion sources in residences, particularly gas-fueled cooking stoves, are strong determinants of total personal exposures to nitrogen dioxide (NO_2) (Quackenboss et al. 1986; Ryan et al. 1988b, 1990). Typically, for people living in homes with gas cooking stoves, NO_2 exposures in residences are higher than those experienced in outdoor settings or public buildings (Quackenboss et al. 1986). For population groups that spend the majority of their time indoors at home, such as infants and preschool-age children, the time-weighted contributions of exposures received indoors at home dominate total personal exposure (Hoek et al. 1984; Harlos et al. 1987).

The assessment of effects of NO_2 on the respiratory health of children requires accurate estimates of personal exposures. The inconsistent epidemiologic evidence of association between the presence of unvented gas cooking stoves and adverse respiratory outcomes in children in published studies may be explained in part by misclassification of exposure (Samet et al. 1987; Samet and Utell 1990). In this report, we describe the exposure assessment methodology in a prospective cohort study of NO_2 and respiratory infection conducted in Albuquerque, NM. The accompanying report, Part I: Health Outcomes (Samet et al. 1993) provides the findings with regard to NO_2 exposure and health.

* A list of abbreviations appears at the end of this report for your reference.

This Investigators' Report is Part II of the Health Effects Institute's Research Report Number 58, which also includes Part I (an Investigators' Report by Samet and colleagues), a Commentary on both Investigators' Reports by the HEI Health Review Committee, and an HEI Statement about the research project. Correspondence regarding the Investigators' Report by Dr. Lambert and associates may be addressed to Dr. William E. Lambert, New Mexico Tumor Registry, University of New Mexico Medical Center, 900 Camino de Salud NE, Albuquerque, NM 87131-5306.

This study was supported by funds from the U.S. Environmental Protection Agency, the motor vehicle industry, and the Gas Research Institute. Although this document was produced with partial funding by the EPA under assistance agreement 816285 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 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.

SPECIFIC AIMS

The principal objective of this component of the prospective study was to characterize the NO_2 exposures of infants and to develop measures of exposure appropriate for testing the relation between NO_2 exposure and respiratory illness. The protocol for monitoring NO_2 exposures was based on the results of previously reported pilot investigations (Harlos et al. 1987; Samet and Spengler 1989). Exposures were to be assessed by making measurements of NO_2 concentrations in the homes of the subjects using passive diffusion samplers. For each subject, a series of NO_2 measurements was to be obtained from birth to the age of 18 months. Information on the activity (location) patterns of the infants and stove use would also be acquired. The specific goals of this monitoring were: (1) to provide repeated measurements of home NO_2 concentrations that could be used to estimate the longitudinal and cumulative exposures of individual subjects; (2) to characterize opportunities for exposure to elevated concentrations of NO_2 associated with stove use; and (3) to evaluate the extent to which time-activity patterns and room-to-room variation in NO_2 concentrations may influence infants' residential exposures.

METHODS AND STUDY DESIGN

OVERVIEW OF THE MONITORING PROTOCOL

The hypotheses to be tested in the cohort study required monitoring each child's exposure to NO_2 for the first 18 months of life (Samet et al. 1992). It was not practical to place passive samplers on the subjects' clothing because movement could block the sampler's opening; furthermore, the parents would have needed to place the samplers on the infants daily. Therefore, based on experience in pilot studies (Harlos et al. 1987; Samet and Spengler 1989), we assumed that residential exposures represented the dominant contribution to total personal exposures for infants and toddlers who did not attend day care away from home for more than 20 hours per week.

To measure NO_2 concentrations, passive diffusion samplers (Palmes et al. 1976) were placed in the subjects' bedrooms and exchanged on a two-week cycle for homes with gas stoves, and on an alternate two-week cycle for homes with electric stoves (Table 1). At two-week intervals, coincident with the exchange of the NO_2 samplers, a standardized telephone interview was conducted to collect information from the parents on the subjects' daily respiratory symptoms and factors influencing residential NO_2 exposure, including cooking range and oven use, time subjects spent in the kitchen during cooking, and time subjects spent away from home. At intervals of 2 months, as part of the routine telephone interviews, the parents were asked to recall the amount of time the subjects spent in various rooms of the house and away from home during the previous 24 hours.

SUBJECT ENROLLMENT AND OBSERVATION

Over 1,300 subjects were enrolled in the study (Samet et al. 1992). Enrollment occurred at the rate of approximately 35 subjects per month. A total of 1,205 subjects were observed for at least 30 days, and 823 subjects completed the full protocol of 18 months of observation (Samet et al. 1993). The monitoring data were collected from January 1988 through December 1991 in 1,416 residences; 180 subjects changed residences during the study.

PASSIVE DIFFUSION SAMPLERS

The passive diffusion samplers, or Palmes tubes (Palmes et al. 1976), were constructed of acrylic plastic with an approximate length of 6.6 cm and internal diameter of 0.9 cm. When the tubes were open to the air, NO_2 was absorbed into triethanolamine that had been applied to stainless-

Table 1. Schedule of Nitrogen Dioxide Monitoring

Sampling Site	Monitor Rotation Schedule
Homes with gas cooking ranges	
Bedroom	Consecutive two-week samples, year-round
Living room	Two-week samples in September, November, January, and March
Kitchen	Two-week samples in September, November, January, and March
Homes with electric cooking ranges	
Bedroom	Alternate two-week samples, year-round
Outdoors	
11 Sites	Consecutive two-week samples, year-round

steel screens located at the closed end of the tube. The amount of absorbed NO_2 was quantified by spectrophotometric analysis and sulfanilamide was used as a color-forming reagent. Light absorbance at 540 nm was calibrated against standards made of sodium nitrite, using conventional methods of serial dilution. The amount of absorbed nitrite was converted to airborne NO_2 concentration equivalents, using Fick's law and assuming an indoor diffusion rate of 0.154 cm^2/sec.

The Palmes tubes were produced by the Air Quality Laboratory at the Harvard School of Public Health. They were assembled in batches of 33 tubes; from each batch, three tubes were pulled for colorimetric analysis before shipment to the University of New Mexico. If the net absorbance of any of the three tubes exceeded a quality control absorbance level, the batch was disassembled.

The Palmes tubes were labeled with bar codes at the University of New Mexico and assembled into packages for use by the research subjects. After the initial placement of tubes in the homes by field technicians, exchanges of the tubes were conducted by mail. Parents returned tubes to the University of New Mexico using a postage-paid mailing tube. Upon receipt of the tubes, the bar-code labels were optically scanned and information on the dates and times of tube opening and closing was keyed into the computer. The data-entry software included range and logic checks to reduce errors. The tubes were assembled into batches of approximately 400 and sent to Harvard School of Public Health for analysis.

When received at Harvard, tube labels were optically scanned, and the inventory was compared with the shipping list produced by the University of New Mexico. Before each session of analysis, nitrite standards were prepared and analyzed. The calibration curve was required to fall within quality control limits based on the experience of the Harvard laboratory. The spectrophotometric analysis was semiautomated and involved the use of a carrousel to handle tubes, a sipper to deliver the reagent to the cuvette in the spectrophotometer, and software to calculate nanomoles of NO_2 (nitrite) from absorbance values and to calculate the integrated average using duration times. Field blank values were subtracted from measurements to correct for NO_2 contamination occurring during assembly and handling of the tubes. As a quality control measure, between- and within-home comparisons were made to identify homes with potential monitoring problems. Measurements were considered to be suspicious if they were below the limit of detection (2 ppb), were very high (greater than 150 ppb), or deviated from the expected room-to-room gradients (i.e., kitchen greater than activity room greater than bedroom). In turn, this information was used by the University of New Mexico field staff to identify households requiring extra guidance in the use of the sampler tubes.

HOME MONITORING PROTOCOL

The monitoring protocol varied with the type of cooking stove present in the home and the season (Table 1). In homes with gas stoves, consecutive two-week samples were obtained in the subjects' bedrooms throughout the year. During the heating season (in September, November, January, and March), two-week measurements were made in the kitchen and the activity room. In homes with electric stoves, bedroom concentrations were measured during every other two-week period, year-round.

The sampler tubes were originally placed in the homes by field technicians. Tubes were located 3 to 6 feet above the floor, at least 3 feet away from windows and exterior doors, and at least 6 feet away from potential NO_2 sources (e.g., stoves, furnaces, gas space heaters). Wherever possible, tubes were placed away from surfaces with a potential for NO_2 removal (e.g., drapery, brick walls, house plants), away from fans, and away from dead spaces (i.e., stagnant air spaces such as corners or the back of bookshelves). When opened, the sampler tubes were hung open end down, in metal racks or by clips with plastic collars. The placement of the tubes was documented with diagrams of room layouts and brief word descriptions. The parents were instructed to maintain the tubes in these agreed upon locations. Subsequent exchanges of the tubes were handled by mail. New sets of tubes were mailed out ahead of the routine phone call to collect health symptom information, and the tubes were exchanged as part of the telephone interview. Each new set of tubes was accompanied by written instructions describing the proper use of the sampler tubes. Prior to September of 1990, the tubes were identified by number and cap color; after that time, additional labels were used to identify the room in which the tube was to be placed (i.e., BED, ACT, and KIT).

OUTDOOR MONITORING PROTOCOL

Outdoor measurements of NO_2 were made by placing passive samplers at each of the 11 ambient air monitoring sites operated by the City of Albuquerque Department of Environmental Health (Figure 1). These monitoring sites are maintained to meet federal requirements for urban area monitoring. Various criteria pollutants are measured at these sites, and the data are submitted to the U.S. EPA's Aerometric Information Retrieval System. Of the 11 monitoring stations, the city monitors NO_2 at only one site located in the densely populated northeast area. At this station, NO_2

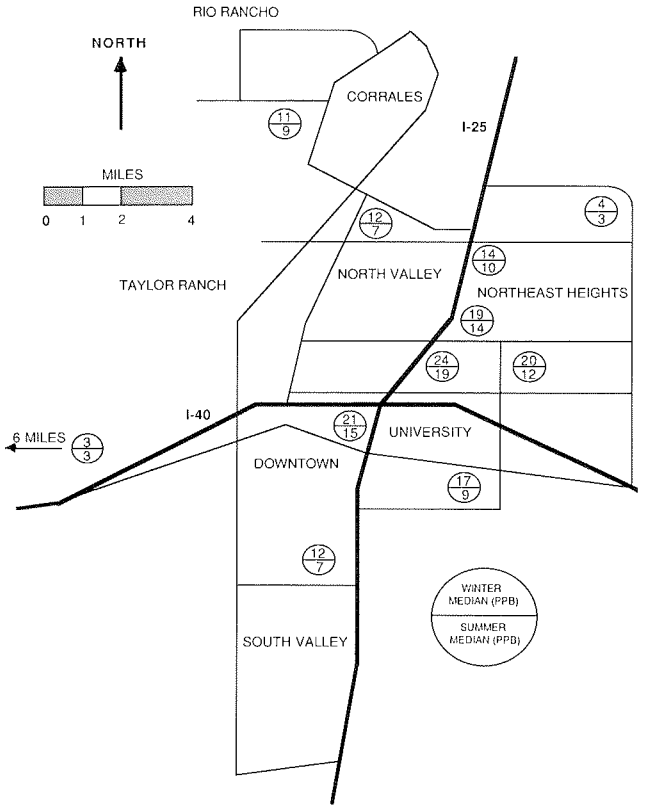


Figure 1. Spatial distribution of winter/summer median NO_2 concentrations measured at 11 ambient air monitoring sites in Albuquerque, NM, 1988 to 1991. Values are given in ppb for winter/summer.

is continuously measured by gas-phase chemiluminescence. Most of the stations are located in urban areas near the residences of the subjects participating in this study. However, passive diffusion sampler measurements of NO_2 were also made at two "far-field" sites located nine miles to the west of the city and in the far northeast heights where housing has not been built and traffic activity is lower than in the more central areas of the city.

Outside of each station, NO_2 samplers were placed in shelters consisting of metal cans (13 cm in depth by 11 cm in diameter). The shelters were usually hung on the chain-link fence surrounding the building that houses the city's monitoring instrumentation. The shelters were placed approximately 6 feet above the ground and were hung on the inner side of the fence for protection against vandalism and theft. The original placement of the shelters was performed by the Project Coordinator.

Consecutive two-week samples were obtained throughout the course of the study. During the first three years of the study, the samplers were exchanged by the city's air quality monitoring technicians, who had received instruction on the use of the samplers from the Project Coordinator; project personnel performed the exchanges during the final year of the study.

QUALITY CONTROL OF NITROGEN DIOXIDE MEASUREMENTS

Quality control activities may be defined as procedures to monitor and maximize the accuracy of routine measurements. As part of the NO_2 monitoring protocol, 5% of the total number of sampler tubes were deployed as replicates to assess measurement precision. We present data on replicate measurements only for the bedrooms because more pairs are available on a year-round basis for bedroom measurements, and comparable data were obtained in the kitchen and living room. For the 1,975 pairs of tubes placed in bedrooms of homes with gas and electric stoves, the absolute differences were log normally distributed. The median difference was 1.5 ppb, and the mean difference was 3.0 ppb (SD = 5.8 ppb). Ninety-five percent of the replicates differed by less than 11.4 ppb, and the maximum difference was 116 ppb. The more extreme differences in replicates cannot be explained by routine data collected on sampler tube use, and we postulate that the differences are due to some form of error in the use of the samplers by the families. The Pearson correlation (r) between paired measurements was 0.92.

Additionally, 5% of the tubes were deployed as field blanks. These tubes were never opened and accompanied the sampler tubes through all stages of handling, including being sent to the subjects' homes. Using the deployment times of the tube sets, the mean concentration of the 2,388 field blanks was 0.6 ppb and the standard deviation was 4 ppb. The average number of nanomoles of nitrite absorbed by field blanks was subtracted from the measurement values of the batch constructed on the same date to correct for contamination during handling.

The series of bedroom measurements for each residence was screened to detect outlying values using distribution and seasonal criteria. The criteria for identification of outliers were modeled after those used to construct the Tukey box plot (Tukey 1977). An outlier was defined as a value whose distance from the first or third quartile was greater than three times the interquartile range. Seasonal distributions were established for each residence, and the criteria were applied only if six samples were available for the home during that season. Once identified, these outliers were excluded if they failed to meet several criteria for "reasonable" behavior, based on our experience and other published data on the performance of Palmes tubes (Boleij et al. 1986). In homes with gas stoves, outliers were excluded if they differed from the winter or summer median by 25 ppb. During the holiday season, November 10 to January 15, a 40-ppb variance was allowed. In homes with electric stoves, a

10-ppb variance from the winter or summer median was allowed. If an unvented kerosene space heater was present in the home, a 50-ppb variance was used. In order to account for the limit of detection, absolute minima of 1 ppb and −2 ppb were set for tubes from homes with gas and electric stoves, respectively. The rationale for absolute minima is based on the limit of detection of 320 ppb·hours reported by Boleij and associates (1986) and our average tube deployment time of 15 days.

Of a total 32,326 bedroom tubes, 692 tubes (2%) were below the limits of detection and were excluded. Another 3,252 tubes (10%) were excluded because we had knowledge that the tubes were not opened by the mothers or were opened at the wrong time (e.g., duplicate). Of 302 observations (1% of total) identified as outliers by the screening criteria, 145 (less than 0.5% of total) were excluded.

QUALITY ASSURANCE OF NITROGEN DIOXIDE MEASUREMENTS

Quality assurance activities may be defined as assessments of accuracy using methods of measurement that are independent of those routinely used. In order to evaluate the quality of the NO_2 measurements made by the mothers, technicians visited homes to assess the mothers' use of the passive sampler tubes and to deploy a separate set of samplers. During August and September of 1990, 192 homes with gas stoves and 26 homes with electric stoves were randomly selected for this audit from the total 400 homes under observation at that time. We limited selection of participants to those families that would still be under observation during the following winter. In February and March of 1991, 153 gas and 24 electric stove homes of the original group were audited a second time.

Audit visits occurred within the two days following a regularly scheduled biweekly telephone call. Mothers were not informed that the technicians would be assessing their use of the sampler tubes; rather, they were told only that "a technician would be visiting their home to make extra air pollution measurements." During the home visit, the mothers' tubes were left in place and not altered by the technician. A checklist was used to document aspects of the mothers' use of the tubes (e.g., moved from original placement, placed in dead-air space, or near potential NO_2 source). The technicians placed a separate set of tubes in the homes according to standard operating procedures. Two weeks later, after the next telephone interview, the technicians returned to the homes to perform another audit and to retrieve the comparison set of tubes. If necessary, the placement or use of the samplers was corrected with the parents. This approach allowed assessment of the mothers' compliance with monitoring protocols and allowed some quantification of the NO_2 measurement error.

EXTERNAL QUALITY ASSURANCE PROGRAM

The Health Effects Institute contracted an independent organization, Arthur D. Little and Associates, to perform quality assurance audits on the study. Audits of the NO_2 sampler use and handling, laboratory analysis, and data processing were performed at the University of New Mexico and the Harvard School of Public Health. The audits were conducted by the Quality Assurance Officer, Denise Hayes, and Dr. Robert O'Neil, who periodically reviewed standard operating procedures, observed activities on home visits and in the laboratories, and examined data processing. The findings of site visits were directly reported to the Health Effects Institute. The external quality assurance report is included in Appendix C of Part I.

ASSESSMENT OF STOVE USE AND INFANTS' TIME-ACTIVITY PATTERNS

Use of the range burners and oven during the previous 24 hours was assessed during the biweekly telephone call. Additionally, parents reported the time their children spent in the kitchen while the stove was in use. At intervals of two months, during the regular biweekly telephone call, parents were asked to recall the time spent by the subject in the bedroom, kitchen, living room and other rooms, and out of the home. Time-activity patterns were assessed to the nearest 15 minutes, and recall was conducted in chronological order, hour-by-hour, from 5 a.m. on the previous day to 5 a.m. the morning of the call. The assessment of time-activity information by recall interview has been shown to produce data comparable to that obtained with concurrent written diaries (Robinson 1988).

STATISTICAL METHODS AND DATA ANALYSIS

Using the microenvironmental model (Duan 1982), average personal exposures were calculated by the formula

$$E = \frac{\Sigma c_i t_i}{\Sigma t_i}$$

where the personal exposure E is the time-averaged exposure, c_i is the NO_2 concentration associated with a specific setting, and t_i is the average time reported for the subject in that setting. Concentration measurements in four microenvironments were used to model the exposures of infants: kitchen, bedroom, living room and other rooms, and away from home.

The average NO_2 exposure for time spent away from the

home was assumed to be 15 ppb. This microenvironmental class represents the time spent in other people's residences, in public buildings, in motor vehicle travel, and outdoors. The choice of 15 ppb was based on a literature review of the relations between personal and microenvironmental measurements of NO_2 and the average ambient NO_2 concentration measured in homes and at outdoor sites in Albuquerque. The use of the microenvironmental model was validated in the pilot studies (Harlos et al. 1987; Samet and Spengler 1989); in these studies, estimates of total personal exposure derived from microenvironmental monitoring were compared with measurements of monitors worn by the infants (Harlos et al. 1987). In the analysis of Harlos and colleagues, a value of 12.2 ppb was assumed for the out-of-home microenvironment, and good concordance with personal measurements was obtained. In Albuquerque, the mean winter NO_2 level in homes with electric stoves, 7 ppb, is approximately half that observed outdoors, 15 ppb (Figure 2). Public buildings, with the exception of restaurants, typically do not have unvented combustion sources indoors and would be expected to have average NO_2 concentrations similar to those measured in homes with electric stoves. Concentrations in the passenger compartments of motor vehicles would be expected to be 50% higher than nearby ambient concentrations, as predicted by data on Los Angeles commuters (Baker et al. 1990). Time spent in other homes would be expected to result in exposures within the range observed in the homes of the infants, which was 7 ppb to 35 ppb. In light of this potential range of exposures experienced during time away from home, we assumed the mix of exposures to average approximately 15 ppb, and this value was used in the microenvironmental model.

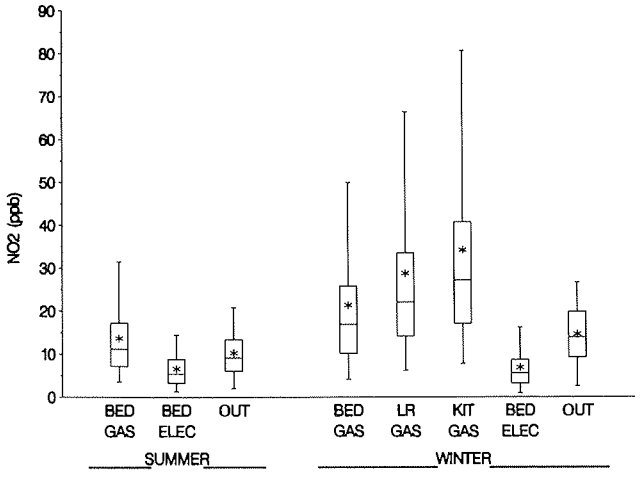


Figure 2. Distribution of outdoor and indoor NO_2 concentrations by type of cooking stove, room, and season. The distributions were computed for all available measurements made in summer (April through September) and winter (October through March). The box and whisker plots show the 25th and 75th percentiles as the bottom and top edges of the boxes, respectively. The medians and means are indicated by the horizontal lines and asterisks, respectively. The vertical lines extend to the 5th and 95th percentiles of the distributions. BED = bedroom, LR = living room, KIT = kitchen, OUT = outdoors, GAS = home with gas cooking stove, ELEC = home with electric cooking stove.

The time-activity data during the period from September to March were averaged for each subject, and the personal exposures were calculated using each subject's average time-activity pattern. By averaging the three to four time-activity assessments available for each subject, we obtained a more stable measurement of the usual winter time-activity pattern. The time-weighted personal exposures were compared with bedroom measurements.

Only a portion of the entire NO_2 exposure data set was used to evaluate the time-weighted personal exposures. In order to standardize the relative contribution of each subject's observation time, only subjects who lived at least one complete winter in a home with a gas stove were used. Because of differences in the timing of enrollment, data from the first complete winter of participation were used. A total of 587 subjects provided data meeting these criteria; these subjects had lived in 56% of the total 1,050 residences with gas cooking ranges monitored during the course of the study. The household characteristics of the group of homes used in this analysis were similar to those of the full sample of all homes with gas stoves. During the winter observation times, time-activity patterns and NO_2 levels were measured in the living room and kitchen every other month. The mean number of NO_2 tube sets was 3.3 per subject (SD = 0.8), and the mean number of time-activity records was 3.6 per subject (SD = 1.0). The number of two-week intervals with simultaneous bedroom, living room, and kitchen measurements was 1,937.

Data management and statistical analyses were performed using the Statistical Analysis System (Version 6, SAS Institute, Cary, NC).

RESULTS

SAMPLE CHARACTERISTICS

The characteristics of the 1,416 homes monitored are presented in Table 2. The majority of residences (73%) were single-family, unattached dwellings with a median size of 1,200 square feet. Most homes were heated by gas, with a central forced air distribution system. Only 26 households (2%) reported owning an unvented kerosene or gas space heater that was used inside the home. Twenty-six percent of residences had electric cooking ranges, 44% of homes had gas ranges with continuously burning pilot lights, and 30% of homes had gas ranges with electronic ignition or burners that were lit with matches. Homes with gas cooking

Table 2. Characteristics of Homes Monitored for Nitrogen Dioxide Concentration[a]

Characteristic	Percentage of Total
Type of home	
Single-family, not attached	73
Apartment	14
Mobile home	8
Other	5
Area of living space	
< 1,000 sq. feet	32.3
1,000–1,499 sq. feet	34.9
> 1,500 sq. feet	32.8
Stove type	
Electric	26
Gas, continuous pilot	44
Gas, no pilot	30
Main heating system	
Central forced air furnace	78
Wall, gravity, floor furnace	16
Electrical units	1
Wood, solar, other	5
Main heating fuel	
Electric	2
Natural gas	95
Wood, solar, other	3
Kerosene space heater present	2

[a] A total of 1,416 separate residences were monitored; 180 subjects changed residences during the study.

Table 3. Characteristics of Occupants from Households Monitored for Nitrogen Dioxide Concentration[a]

Characteristic	Percentage of Total
Number of residences occupied	
1	85
2	12
⩾ 3	3
Number of persons in household	
2	< 1
3	32
4	35
⩾ 5	32
Mother's education (years)	
⩽ 12 Years	35.7
13–15 Years	34.2
⩾ 16 Years	30.1
Hispanic mother	32
Annual household income (dollars)	
< $10,000	10
$10,000–$19,999	21
$20,000–$29,999	23
$30,000–$39,999	20
⩾ $40,000	24
Refused/no answer	2

[a] A total of 1,205 subjects and their households were monitored for at least 30 days.

ranges tended to be smaller, and the majority were either apartments or mobile homes (Samet et al. 1993).

The household characteristics of the 1,205 families are presented in Table 3. Eighty-five percent of the families lived in one home during their participation in the study. Approximately one-third of the households were comprised of two adults and one child. Ninety-five percent of mothers had completed high school, and 35% had some college education. Thirty-two percent characterized themselves as Hispanic. The median annual household income was within the range of $20,000 to $29,999. As reported in the findings of Samet and colleagues (1992), the level of maternal education and household income tended to be lower in homes with gas stoves, and a higher proportion of Hispanic families lived in homes with gas stoves.

FINDINGS OF QUALITY ASSURANCE SURVEY

During the August through September 1990 survey, the overall rate of noncompliance was observed to be low. In 4 of the 214 homes surveyed (2%), the mothers had continued to place the samplers in their own bedroom although the index subject was no longer sleeping in the parents' bedroom. Relative to the samplers placed by the technician in the subjects' bedrooms, the differences in NO_2 concentrations measured by samplers placed by the mothers ranged from −1.9 ppb to 1.3 ppb, with an average of −0.2 ppb. In 24 homes (11%), tubes were judged by the technicians to have been moved by the parents and placed in a dead-air space. In these situations, the difference in measured NO_2 concentrations ranged from −15.8 to 3.9 ppb, with an average of −0.3 ppb. In 27 homes (13%), the proper sampler tubes were not open at the time of the technicians' visits; the delays ranged from several hours to 8 days, with a median delay in opening of 1 day. The resulting differences in measured NO_2 concentrations caused by the delay ranged from −2.3 to 12.4 ppb, with an average of 1.5 ppb. In 20 homes (9%), sampler tubes were not closed at the time of the technicians' return visit. The differences in measured NO_2 concentrations caused by the delay of closing ranged from −1.6 ppb to 3.0 ppb, with an average of 0.7 ppb. Overall, differences in the measurements made by the technicians relative to those made by the mothers ranged from −22.9 to 12.4 ppb, with a mean of 0.3 ppb (SD = 4.0 ppb).

INDOOR NITROGEN DIOXIDE CONCENTRATIONS

The distributions of two-week average NO_2 concentrations inside homes are shown in Figure 2 for "summer" (April through September) and "winter" (October through

March) seasons. During the summer, bedroom NO_2 concentrations in homes with gas stoves averaged 14 ppb (SD = 10 ppb); 5% of the two-week measurements were greater than 31 ppb. In the bedrooms of homes with electric stoves, the summer average concentration was 7 ppb (SD = 6 ppb). Five percent of bedroom measurements in homes with electric stoves were greater than 14 ppb.

During the winter, bedroom concentrations in homes with gas stoves averaged 21 ppb (SD = 22 ppb) (Figure 2). The upper tail of the winter measurement distribution was skewed to the right, with 5% of the two-week measurements exceeding 50 ppb. In bedrooms of homes with electric stoves, winter concentrations averaged 7 ppb (SD = 6 ppb), with 5% of observations exceeding 16 ppb.

During the winter months, living rooms and kitchens in homes with gas stoves were sampled. The average living room concentration was 29 ppb (SD = 48 ppb), and 5% of the two-week average concentrations exceeded 66 ppb (Figure 2). In the kitchen, the average was 34 ppb (SD = 33 ppb); 5% of the kitchen observations were greater than 81 ppb.

The distributions of room-to-room differences in NO_2 concentrations for 3,787 simultaneous bedroom, living room, and kitchen measurements are presented in Figure 3. The differences provide a measure of the concentration gradient within homes. Bedroom concentrations exceeded kitchen concentrations in less than 7% of sampler tube sets. In 10% of tube sets, the mean kitchen-bedroom difference was greater than 25 ppb; in 5% of the tube sets, the difference was greater than 35 ppb.

The correlations among the simultaneous room measurements were high. The Pearson correlation, r, of bedroom and kitchen NO_2 measurements was 0.84, and the bedroom and living room correlation was 0.87. The kitchen and living room correlation was 0.88.

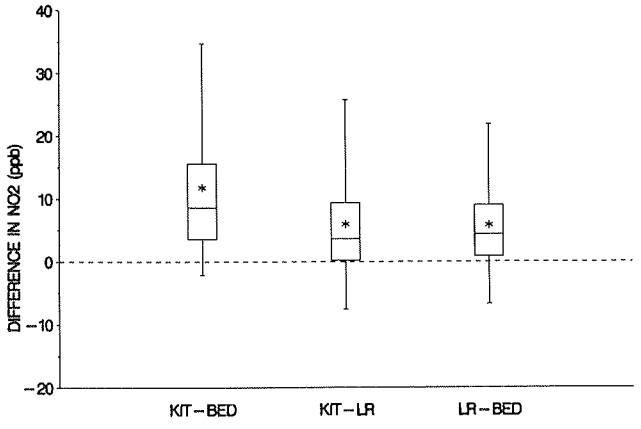


Figure 3. Distributions of absolute differences in NO_2 concentrations between rooms in homes with gas cooking stoves. Data are presented for 3,787 simultaneous sets of measurements obtained during the heating seasons (September through March) of 1988, 1989, 1990, and 1991. The box and whisker plots show the 25th and 75th percentiles as the bottom and top edges of the boxes, respectively. The medians and means are indicated by the horizontal lines and asterisks, respectively. The vertical lines extend to the 5th and 95th percentiles of the distributions. BED = bedroom, LR = living room, KIT = kitchen.

OUTDOOR NITROGEN DIOXIDE CONCENTRATIONS

The average summer concentration for the 11 ambient monitoring sites was 10 ppb (SD = 8 ppb) (Figures 1 and 2); 5% of the two-week measurements exceeded 21 ppb. Ambient concentrations were generally higher in the winter and averaged 15 ppb (SD = 8 ppb). Five percent of the winter observations exceeded 27 ppb.

The spatial distributions of NO_2 levels in Albuquerque for winter and summer seasons during 1988 to 1991 are presented in Figure 1. The winter time median concentrations ranged from 3 ppb at the site located nine miles to the west of the city to 24 ppb at an urban site located in the northeast area of the city, near a major intersection with average daily traffic flows in excess of 40,000 vehicles (Middle Rio Grande Council of Governments 1992).

Median concentrations during the summer averaged approximately 4 ppb less than in winter. The relative ranking of sites by median concentration was similar for winter and summer. During the summer, the median concentrations ranged from 3 ppb at the western remote site to 19 ppb at the northeast urban site.

In summary, the spatial variation in outdoor NO_2 concentrations was greater than the seasonal variation. Inclusion of air monitoring sites on the outskirts of the suburbs and away from the city where concentrations were less than 5 ppb decreased the city-wide average outdoor concentrations. However, the majority of the subjects' homes were located in the suburbs and central areas of the city, where ambient NO_2 levels were highest.

Table 4. Distribution of Time by Location for Infants and Toddlers[a]

	Daily Time (minutes)						
			Percentile				
Location	Mean	SD	5	25	50	75	95
Bedroom	737	111	570	670	733	798	919
Living room	438	130	232	355	436	517	640
Kitchen	35	39	0	5	23	51	116
Out of home	230	116	60	150	218	297	433

[a] Distribution of mean time-activity measures for 1,191 children for whom at least one time-activity interview was completed. A mean of 8.6 time-activity interviews (SD = 3.9) were available for each subject.

TIME-ACTIVITY PATTERNS AND STOVE USE

The distributions of the number of hours spent in the bedroom, kitchen, and the living room and other rooms are presented in Table 4. On average, for all the observations collected during the course of the study, the subjects spent 16% of the day out of the home (three hours and 50 minutes). This percentage includes time spent outdoors, in travel, and in other indoor settings (e.g., public buildings and the residences of others). On average, the subjects spent 51% of the day (12 hours and 17 minutes) in their bedrooms, 31% (7 hours and 18 minutes) in the living room and other rooms of the house, and only 2% in the kitchen (35 minutes). Thus, the total daily time spent inside the home averaged over 20 hours. Small trends in activity patterns, generally less than 20 minutes per day, were observed for all age groups and seasons (Table 5). Total time in the kitchen and time out of the house were higher in the older age groups and during the summer months.

Information on daily stove use and time spent by subjects in the kitchen during stove use is relevant to the evaluation of the subjects' exposures to short-term elevations in NO_2 levels. For 32% of the two-week telephone interviews, mothers reported no range burner use on the previous day (Table 6). Mean daily range burner usage was 29 minutes (SD = 43 minutes); the highest reported use in the previous 24-hour period was 14.8 hours. Oven use was less frequently reported than range burner use; no oven use was reported in 71% of the interviews, and the mean daily usage was 18 minutes (SD = 45 minutes). No differences were observed in stove use or time spent by the subjects in the kitchen for homes with gas and electric stoves. Stove use was observed to increase with family size (data not shown). In 68% of the interviews, parents reported that the subject spent no time in the kitchen when the stove was in use. Mean time spent by subjects in the kitchen when burners or the oven were turned on was nine minutes (SD = 22 minutes).

Parents infrequently reported using the range burners or the oven for space heating. This behavior was assessed on a questionnaire administered at the midpoint and on completion of observation. Only 6% of families reported using the stove to heat their kitchen during the winter months. Approximately 1.5% of families reported using their range burners for heating purposes at least two times per week.

Table 5. Distribution of Mean Time Spent in Locations by Season for Infants and Toddlers

	Mean Daily Time (minutes) by Child's Age		
	0–6 Months	7–12 Months	13–18 Months
Bedroom			
April–September	736	726	730
October–March	742	740	730
Living room			
April–September	442	412	391
October–March	463	450	442
Kitchen			
April–September	24	45	49
October–March	27	41	52
Out of home			
April–September	230	257	267
October–March	208	207	217

Table 6. Distribution of Daily Range Burner, Oven Use, and Infant's Time in Kitchen While Stove Was in Use[a]

	Daily Time (minutes)						
			Percentile				
Stove Use	Mean	SD	5	25	50	75	95
Range burners	29	43	0	0	20	40	90
Oven	18	45	0	0	0	20	90
Infant's time in kitchen during stove use	9	22	0	0	0	10	45

[a] Distributions based on 34,806 observations from 1,205 households.

ESTIMATED TOTAL PERSONAL NITROGEN DIOXIDE EXPOSURES

A total of 1,937 measurement intervals with bedroom, living room, and kitchen NO_2 measurements, and time-activity data were available for comparing the calculated time-weighted exposures versus the bedroom concentration (Table 7). The exposure estimates were stratified into three classes that were identical to those in the analysis of health effects (Samet et al. 1993): low (0 to 20 ppb), medium (20 to 40 ppb), and high (greater than 40 ppb). For these exposure strata, personal exposures based on bedroom measurements were not substantially different from those derived using the microenvironmental model.

Table 7. Cross Tabulation of Time-Weighted Nitrogen Dioxide Exposure Versus Bedroom Concentrations[a]

	Time-Weighted NO_2 Exposure Class		
Bedroom Concentration	Low (0–20 ppb)	Medium (20–40 ppb)	High (> 40 ppb)
Low	1,097	116	1
Medium	28	529	18
High	0	33	115

[a] Based on 1,937 two-week measurement intervals from 587 homes during the winter seasons.

Overall, 90% of classifications were in agreement. Six percent of the divergent classifications occurred in subjects classified as having "low" exposures, based on the bedroom measurements, as compared with "medium" exposures, based on the microenvironmental model. Only one comparison interval with a "low" classification based on bedroom measurements was classified as "high" by the microenvironmental model.

Using linear regression, we further assessed the relationship between the exposure estimate derived from the microenvironmental model and the bedroom concentration. The linear model also demonstrated close agreement:

$$NO_{2\text{Time-Weighted}} = 3.4 + 0.90 \times NO_{2\text{Bed}},\ R^2 = 0.94.$$

The mean difference between microenvironmental exposure estimates and the bedroom concentrations was 1.4 ppb.

DISCUSSION

The NO_2 measurements made in the New Mexico study represent the largest and most comprehensive series of measurements in the indoor setting on this air pollutant. From 1988 to 1991, approximately 36,000 two-week measurements were made inside the homes of 1,205 subjects, and 1,000 measurements were made at 11 outdoor monitoring stations. In this report, we describe indoor concentrations by season and type of cooking stove. Additionally, using the microenvironmental modeling method, the measurements are combined with time-activity data to estimate exposures for the infants and toddlers. A later report will present analyses of physical and behavioral factors that influence indoor NO_2 concentrations cross-sectionally and longitudinally.

QUALITY CONTROL AND QUALITY ASSURANCE

The exposure assessment included extensive quality control and quality assurance procedures. The elements of the program included a written protocol describing the overall study design, documentation of standard operating procedures and technician training, written record keeping, and appropriate data processing and verification procedures (Samet et al. 1992). As part of the quality control and quality assurance program, replicate measurements and field blanks were used to monitor the precision and sensitivity of the passive sampler tubes. Analyses of the blank samples indicated that relatively little background contamination was associated with sampler handling and that limits of detection were low. In general, a high level of concordance was observed between replicate measurements, demonstrating that measurements in the homes were precise. However, some intrapair differences were large and document that the parents of some subjects had problems with adhering to the monitoring protocols.

Because the deployment of the NO_2 samplers was dependent on the parents, a separate series of quality assurance audits was conducted. In 214 homes, low rates of noncompliance were documented, and differences in NO_2 concentration measured by sampler tubes placed by technicians compared with those placed by the mothers averaged less than 1 ppb. The most commonly observed problem was delay in exchanging the sampler tubes, which occurred in approximately 7% of the homes. A delay in opening or closing a set of tubes would tend to lower or raise the calculated NO_2 concentrations. For example, if the mother did not report a two-day delay in exchanging the samplers deployed for 14 days, the calculated NO_2 concentration would be 14% low in the prior series and 14% high in the current series of measurements. Parents were encouraged to inform us if they were unable to exchange the samplers at the time of the phone call; however, we are certain that delays occurred and are a source of variability in the longitudinal series of measurements. The cumulative exposure estimate for each subject would be expected to remain unbiased.

Relatively few measurements, 2%, were eliminated by the statistical quality control procedures used to edit the NO_2 series for each home. The loss of data caused by improper handling of the tubes is comparable to that in other studies that relied on study participants rather than technicians to deploy samplers (Ryan et al. 1988b). Over half of the excluded NO_2 measurements occurred because the mothers informed us that they had not opened the sampler (e.g., forgot to make the exchange or were away from home) and the sampler was not used. Few measurements were excluded because they exceeded limits of detection or acceptable variability.

INDOOR NITROGEN DIOXIDE CONCENTRATIONS

As anticipated from the pilot studies (Harlos et al. 1987; Marbury et al. 1988) and findings from other studies (Quackenboss et al. 1986; Ryan et al. 1988b; Spengler et al. 1990), indoor concentrations of NO_2 were consistently higher in homes with gas cooking stoves than in homes with electric stoves. In our sample of Albuquerque homes, winter concentrations in homes with gas stoves averaged 14 ppb higher than levels in homes with electric stoves. During the summer, the difference was less pronounced; NO_2 concentrations in homes with gas stoves averaged 7 ppb higher than levels in homes with electric stoves.

In these homes, indoor to outdoor concentration ratios were similar to those reported for homes in other U.S. cities (Drye et al. 1989). Typically, in homes with gas stoves, in-

door NO_2 concentrations exceed outdoor concentrations, but homes with electric stoves have lower indoor concentrations than those found outdoors. In the Albuquerque homes, the mean winter indoor-to-outdoor ratio was 1.4, and the mean summer ratio was 1.3 for homes with gas stoves. In homes with electric stoves, the mean indoor-to-outdoor ratio was lower in the winter (0.5) than in the summer (0.7). These trends reflect the accumulation of NO_2 generated indoors during the winter, when the exchange of indoor and outdoor air is reduced, and the increased exfiltration of indoor-generated NO_2 during the summer, when air exchange rates increase.

Large seasonal differences in air exchange rates of homes are assumed because of Albuquerque's climate. Winter daytime temperatures range from 2°C to 15°C, and doors and windows are kept closed to conserve heat. Measurements of whole-house air exchange rates made in 43 homes during the winter in the pilot studies (Samet and Spengler 1989) characterized a low range of air exchange rates, 0.2 to 2.2 air changes per hour, with a median of approximately 0.3 air changes per hour. During the summer, air exchange rates are expected to be high due to the use of natural and mechanical ventilation. Daytime temperatures in Albuquerque range from 20°C to 35°C, and evaporative coolers are used in most homes to reduce indoor temperatures. Windows are usually kept open while the evaporative coolers are in use. The air delivery rates of evaporative coolers range from 3,300 to 9,000 cfm. The capacity of most units sold in Albuquerque is approximately 4,800 cfm; therefore, relative to the median home volume, 9,600 cubic feet, this air delivery rate is large.

The wintertime NO_2 concentrations measured inside Albuquerque homes with gas stoves are generally in the middle of the range of concentrations reported for U.S. homes (Table 8). Concentrations in the Albuquerque homes were comparable with those measured in Portage, WI (Quackenboss et al. 1986), Kingston-Harriman, TN (Neas et al. 1991), St. Louis, MO, and Watertown, MA (Drye et al. 1989). However, the Albuquerque measurements were lower than those in Boston, MA (Ryan et al. 1988b, 1990) and Los Angeles, CA (Spengler et al. 1990). The NO_2 concentrations measured in Los Angeles homes have been attributed to relatively high ambient concentrations and the entry of ambient NO_2 with air exchange (Drye et al. 1989; Spengler et al. 1990).

As expected, we observed room-to-room differences in NO_2 concentration in homes with gas stoves. However, the gradients were relatively small throughout the two-week averaging times of the passive samplers. Decreases in room concentration relative to distance from the kitchen have been observed in other studies (Lebret 1985; Quackenboss et al. 1986; Harlos 1988) and can be attributed to dilution, chemisorption, and exfiltration.

Table 8. Nitrogen Dioxide Concentrations for Gas Stove Homes in Albuquerque and Other Locations[a]

	Mean Concentrations (nearest ppb)		
	Ambient	Bedroom	Kitchen
Albuquerque, NM			
Summer	10	14	—
Winter	15	21	34
Boston, MA			
Summer	22	24	33
Winter	21	25	38
Southern California			
Summer	43	41	55
Winter	62	50	71
Portage, WI			
Summer	6	13	21
Winter	8	23	37
St. Louis, MO			
Summer	5	26	36
Winter	4	31	49
Watertown, MA			
Summer	21	23	30
Winter	22	26	42

[a] Adapted from Drye and coworkers (1989).

OUTDOOR NITROGEN DIOXIDE CONCENTRATIONS

Ambient monitoring data obtained by the passive diffusion samplers are in agreement with continuous monitoring data reported for Albuquerque to the National Air Quality Monitoring Network. Because ambient levels of NO_2 are typically well below the National Ambient Air Quality Standard (NAAQS), NO_2 is continuously monitored at only one site in the city. This station is located in the northeast section of the city, where traffic activity is relatively high. For 1988 and 1989, this monitoring site reported an annual average of 19 ppb to the National Air Monitoring Network. Among the 11 ambient air monitoring stations where we placed passive samplers, this location was consistently associated with the highest concentrations. From 1988 to 1991, the median winter concentration measured by the passive samplers was 24 ppb; the median summer concentration was 19 ppb.

Among the 103 Metropolitan Statistical Areas in the national network for which maximum annual average concentrations were available for 1988 to 1989, Albuquerque ranked at the median interval of 19 ppb to 20 ppb (U.S. Environmental Protection Agency 1990, 1991). In interpreting these data, it should be recognized that the Metropolitan Statistical Areas included were not selected to be representative of the entire United States, and the data for each area represent the monitoring site with the highest annual average. Thus, the distribution of values for the 103 Metropolitan Statistical Areas may overestimate population ex-

posures. Nevertheless, using this distribution for evaluating the generalizability of our findings, we conclude that ambient NO_2 concentrations in Albuquerque are similar to those observed in most urban locations in the United States. This comparison also shows, however, that some urban locations have much higher NO_2 concentrations than Albuquerque. These locations include Los Angeles and a number of eastern and midwestern cities. During the last 10 years, the Los Angeles area was the only area in the United States to violate the NAAQS for NO_2 (U.S. Environmental Protection Agency 1990, 1991).

HIGH INDOOR EXPOSURES

Some residential settings with particularly high indoor NO_2 exposures have been reported. These microenvironments warrant consideration as potential sources of exposure misclassification in the Albuquerque study; to the extent that they are not fully represented in our data, the generalizability of our findings is limited.

Low rates of air exchange and small living spaces have been associated with relatively high indoor levels of NO_2. In the Harlem area of New York City, Goldstein and coworkers (1984, 1988) obtained diffusion sampler measurements in 93 apartments. During several monitoring seasons, mean 48-hour levels in 93 kitchens were found to exceed the NAAQS of 53 ppb. The high levels in these apartments were attributed to the small volumes of the living spaces and low air exchange rates due to brick and stone construction and replacement of window frames to reduce heat loss. High levels of NO_2 have also been reported for public housing in Chattanooga, TN, where poor maintenance and occupant behavior were considered to be possible causes (Parkhurst et al. 1989). In contrast, the housing in our study was largely comprised of detached single-family homes occupied by the owners. We suggest caution in extending our findings to the range of exposures that may be found in inner city apartments and public housing.

Elevated indoor levels associated with use of the gas range or oven for heating have been reported for limited samples of more advantaged urban populations in Chicago, IL (Sterling et al. 1981) and Southern California (Baker et al. 1987). Currently, the nationwide prevalence of this practice is unknown. In the Albuquerque study, the range or oven was used for heating in approximately 6% of homes with gas-fueled stoves.

Unvented kerosene and gas space heaters have also been associated with elevated indoor NO_2 concentrations. These heating appliances have high rates of emissions (Leaderer 1982) and are typically used for extended lengths of time. Indoor levels ranging from 20 ppb to 1,300 ppb have been reported (Leaderer et al. 1986; McCarthy et al. 1987; Dudney et al. 1989). However, use of these heating appliances appears to be less common in Albuquerque than in other regions of the country; approximately 2% of households owned kerosene or gas space heaters that were used inside the residence.

TIME-ACTIVITY PATTERNS AND STOVE USE

The time-activity patterns of the Albuquerque subjects are similar to the available data on the activity and air pollution exposure patterns of infants and preschool-age children. The infants and toddlers averaged about 20 hours per day inside their homes (Table 4). To minimize respondent burden, our methods of data collection did not distinguish among settings outside the home. Presumably, the time was spent outdoors, and in motor vehicles, other people's homes, public buildings, and child-care facilities. In the pilot studies (Harlos et al. 1987; Samet and Spengler 1989), which tracked activities away from home, 13 minutes per day were spent outdoors, and 48 minutes per day were spent in travel.

Restrictions on subject selection inherent in the study design (i.e., day-care attendance less than 20 hours per week and nonsmoking households) may limit the generalizability of the sample for the general population of infants. However, findings of a study of a population-based sample of children living in California from 1987 to 1988 show that all children in this age range spend large proportions of time indoors at home (Wiley 1991) (Table 9). Unlike our study, Wiley's study (1991) did not use the infants' time away from home as a condition of participation; thus, the California sample is representative of the full range of activities pursued by this age group. For 172 boys aged zero to two years, time outside the home averaged 283 minutes per day, or approximately 60 minutes more than the infants and toddlers in our study. Child care away from home averaged 86 minutes per day; time spent in another's home averaged 67 minutes per day; time spent in stores, restaurants, and shopping places averaged 21 minutes per day; and time spent in transit averaged 54 minutes per day. Girls of the same age group spent similar amounts of time in these settings but averaged less time in child care and more time in transit.

In our study, time spent in the kitchen while the stove or oven was in use averaged nine minutes per day. Similar findings were reported in the study of children's activity patterns in California during the same time period (Wiley 1991). For California children, ages zero to two years, average time spent in rooms where a gas cooking stove was in use was 11 minutes per day; stove use with the child in the room was reported on 32% of diary days.

We noted that stove use in the current study appeared to

Table 9. Comparison of Albuquerque Time-Activity Data with California Survey of Children Ages Zero to Two Years[a]

	Mean Daily Time (minutes per day)		
	Albuquerque	California	
Location	1,205 Boys and Girls	172 Boys	141 Girls
Home	1,210	1,157	1,151
Outside the home[b]	230	282	287
Day care	—	86	59
Other homes	—	67	56
Stores, restaurants	—	21	23
In transit	—	54	76
Other locations and outdoors	—	54	73
Child's time in kitchen during stove use	9	10	12

[a] Data from survey of children's activity patterns conducted by the California Air Resources Board during 1987 to 1988 on a population-based sample of California children (Wiley 1991).

[b] In the Albuquerque study, times spent in specific settings away from home were not measured.

be less than that observed in the pilot studies (Marbury et al. 1988; Samet and Spengler 1989). For 144 homes monitored in 1984, range burners were estimated to be used 6.1 days per week for cooking dinner, 2.9 days for lunch, and 4.7 days for breakfast. Ovens were used approximately three days per week in these earlier studies. In the current study, conducted four to eight years later than the pilot studies, some range burner use during the previous day was reported in 68% of telephone interviews, a frequency of 4.8 of every 7 days, and some oven use was reported in 29% of calls, or approximately two of every seven days. The apparent trend of decreasing stove use may be related to the use of microwave ovens. In the pilot studies, 26% of gas stove homes and 51% of electric stove homes had microwave ovens. Four years later, in the current study, approximately 90% of homes with gas and electric stoves had microwave ovens.

ESTIMATION OF PERSONAL EXPOSURES

Accurate estimates of personal exposures are required for the evaluation of the effects of NO_2 on respiratory health. Estimates of risk may be biased by the misclassification of exposure. Measurement error and its consequences for estimates of effect, although not unique to air pollution epidemiology, have been widely recognized as a limitation of the epidemiologic approach to investigating air pollution (National Research Council 1985). Error introduced by misclassification can distort correlation or regression coefficients (Shy et al. 1978; Brunekreef et al. 1987) and estimates of relative risk (Copeland et al. 1977; Ozkaynak et al. 1986).

In many epidemiologic studies of the health effects of NO_2, simple classifications of exposure, based on the presence or absence of a gas cooking stove, were used (Samet et al. 1987). The potential for misclassification is substantial with this categorical approach. The low end of the range of NO_2 concentrations in homes with gas cooking stoves overlaps that of the upper end of the concentration distribution for homes with electric stoves. Presumably, this overlap is due to the presence of other indoor sources, variation in the use of gas stoves, the rate of exchange of indoor and outdoor air, ambient concentrations, and house volume (Spengler et al. 1983). More accurate exposure classification has been achieved by direct measurements of NO_2 (Florey et al. 1979; Melia et al. 1982; Hoek et al. 1984; Fischer et al. 1985; Berwick et al. 1989; Neas et al. 1991). Because direct measurements increase the expense and complexity of data collection, these latter studies relied on one or a few residential measurements to classify longer term exposure.

The accuracy of sampling for characterizing residential NO_2 exposure has been evaluated for epidemiologic investigations in the Netherlands (Brunekreef et al. 1987; Houthuijs et al. 1990) and in the current study (Lambert et al. 1992). Misclassification can be reduced by repeated measurements and by optimizing the timing of samples. In this study (Lambert et al. 1992), the average probability of misclassification of a home's winter mean concentration averaged 17% for a single two-week measurement during the winter season and 10% for three measurements. The estimated probability of misclassification decreased to 5% for the continuous series of two-week samples that we attempted to obtain from each home.

The measured personal exposures of adults, children, and infants have been demonstrated to be highly correlated with average indoor NO_2 concentrations and personal exposures estimated by the microenvironmental method (Noy

et al. 1986; Quackenboss et al. 1986; Harlos et al. 1987; Schwab et al. 1990). Although these microenvironmental models generally have been successful at predicting the mean of the distribution of directly measured personal exposures, the models tend to underestimate the upper tail of the distribution. However, the analyses of Quackenboss and associates (1986) on data from adults and the analyses of Harlos and associates (1987) on our pilot study data from infants indicate that, overall, accuracy is not greatly affected by using indoor (bedroom) concentrations as a surrogate measure of total personal exposure.

In the Albuquerque sample of infants, calculation of personal exposures based on time-activity data and room concentrations did not produce estimates of exposure that were substantially different from those represented by the bedroom concentrations (Table 7). Ninety percent concordance was demonstrated for the two methods of assigning exposure, supporting the choice of the bedroom NO_2 concentration to represent the infants' and toddlers' total exposures to NO_2. As found by other investigators using this approach (Hoek et al. 1984; Quackenboss et al. 1986; Schwab et al. 1990), there was a small tendency of the bedroom concentrations to underestimate total personal exposures. Agreement of the two methods was generally higher in the Albuquerque study than in these other studies, a finding that may be attributed to a more homogeneous sample created by the restriction of the subject group to infants and toddlers, ages 0 to 18 months, who did not attend day care for more than 20 hours per week.

CONCLUSIONS

The winter NO_2 concentrations measured inside Albuquerque homes with gas stoves are in the middle of the range reported for other cities in the United States. As expected, indoor concentrations were found to be higher in homes with gas stoves than in homes with electric stoves, and indoor concentrations were higher during the winter season than in the summer. We also established that in homes with gas stoves, average NO_2 concentrations are highest in the kitchen; however, the room-to-room differences in NO_2 concentrations are not large. As reported by the parents, stove use averaged less than 30 minutes per day, and infants infrequently spent time in the kitchen while the stove was in use, indicating that opportunities for exposure to elevated NO_2 levels associated with cooking were small.

The distribution of exposure estimates derived from the microenvironmental model implies that kitchen exposures, relative to exposures experienced in other rooms of the home or settings away from home, contribute little to infants' total exposure to NO_2. Because infants and toddlers meeting the selection criteria for our study spent large amounts of time in their bedrooms and other rooms of the house with similar average concentrations, measurements of bedroom concentrations provided adequate estimates of residential exposures.

These findings are consistent with the results of earlier pilot studies (Harlos et al. 1987) and studies in the Netherlands (Hoek et al. 1984; Noy et al. 1986). Although the use of average concentrations in the bedroom probably underestimates exposures because some high exposures occur during times when the stove is in use and during travel in motor vehicles, the infants participating in this study did not spend extensive periods of time in these situations. In Albuquerque, infants and toddlers who live in homes with gas stoves are infrequently exposed to high, sustained concentrations of NO_2, and the relevant time-scale of exposure for epidemiologic research is the longer term average, which is adequately represented by the bedroom concentration.

ACKNOWLEDGMENTS

We are grateful for the conscientious efforts of the Albuquerque families that participated in this research. We thank the members of the field study team at the University of New Mexico (Kay Browning, Diane Corry, Genevieve Degani, Pamela England, Dawn Hamilton, Louise Kahn, Veronica Ketchbaw, Val King, Anna Kratochvil, Teri Law, Dona Lewis, Beth Meysenberg, Bella Montgomery, Emilie O'Mara, Delinda Scenters, and Anna Reade) for their energy and enthusiasm, diligence, and attention to detail. We also thank the members of the Air Quality Laboratory at the Harvard School of Public Health (Robert DeVivo, David Harlos, Beth Owens, Jenny Su, and Lauri Wast) for their careful analyses of the many thousands of NO_2 samplers used in this study.

REFERENCES

Baker PE, Beals SA, Cunningham SJ, Colome SD, Wilson AL, Shikiya D. 1990. Measurements of personal nitrogen dioxide exposure inside automobiles while commuting. In: Combustion Processes and the Quality of the Indoor Environment (Harper JP, ed.) pp. 149–150. Air and Waste Management Association, Pittsburgh, PA.

Baker PE, Cunningham SJ, Becker EW, Colome SD, Wilson AL. 1987. Evaluation of housing and appliance characteristics associated with elevated indoor levels of nitrogen dioxide. In: Indoor Air '87, Proceedings of the 4th International

Conference on Indoor Air Quality and Climate, Vol. 1, Volatile Organic Compounds, Combustion Gases, Particles and Fibres, Microbiological Agents (Seifert B, Esdorn H, Fischer M, Rüden H, Wegner J, eds.). Institute for Water, Soil, and Air Hygiene, Berlin, Germany.

Berwick M, Leaderer B, Stolwijk JA, Zagranisk RT. 1989. Lower respiratory symptoms in children exposed to nitrogen dioxide from unvented combustion sources. Environ Int 15:369–373.

Boleij JSM, Lebret E, Hoek F, Noy D, Brunekreef B. 1986. The use of Palmes diffusion tubes for measuring NO_2 in homes. Atmos Environ 20:597–600.

Brunekreef B, Noy D, Clausing P. 1987. Variability of exposure measurements in environmental epidemiology. Am J Epidemiol 125:892–898.

Copeland KT, Checkoway H, McMichael AJ, Holbrook RM. 1977. Bias due to misclassification in the estimation of relative risk. Am J Epidemiol 105:488–495.

Drye EE, Ozkaynak H, Burbank B, Billick IH, Baker PE, Spengler JD, Ryan PB, Colome SD. 1989. Development of models for predicting the distribution of indoor nitrogen dioxide concentrations. J Air Waste Manage Assoc 39:1169–1177.

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

Dudney CS, Hawthorne AR, Monar KP, Cohen MA, Spengler JD. 1989. Impact of kerosene space heater usage on indoor NO_2 exposures in 50 east Tennessee homes. In: Combustion Processes and the Quality of the Indoor Environment (Harper JP, ed.) pp. 131–148. Air and Waste Management Association, Pittsburgh, PA.

Fischer P, Remijn B, Brunekreef B, Van der Lende R, Shouten J, Quanjer P. 1985. Indoor air pollution and its effect on pulmonary function of adult non-smoking women: II. Associations between nitrogen dioxide and pulmonary function. Int J Epidemiol 8:347–353.

Florey C du V, Melia RJW, Chinn S, Goldstein BD, Brooks AG, John HH, Craighead IB, Webster X. 1979. The relation between respiratory illness in primary school children and the use of gas for cooking: III. Nitrogen dioxide, respiratory illness and lung infection. Int J Epidemiol 8:347–353.

Goldstein I, Hartel D, Andrews L. 1984. Indoor exposure of asthmatics to nitrogen dioxide. In: Indoor Air, Proceedings of the 3rd International Conference on Indoor Air and Climate, Vol. 2 (Berglund B, Lindvall T, Sundall J, eds.) pp. 269–274. Swedish Council for Building Research, Stockholm, Sweden.

Goldstein IF, Andrews LR, Hartel D. 1988. Assessment of human exposure to nitrogen dioxide, carbon monoxide, and respirable particulates in New York inner-city residences. Atmos Environ 22:2127–2139.

Harlos DP. 1988. Acute Nitrogen Dioxide Exposure During Cooking or Commuting (doctoral dissertation). Harvard School of Public Health, Boston, MA.

Harlos DP, Marbury M, Samet J, Spengler JD. 1987. Relating indoor NO_2 levels to infant personal exposures. Atmos Environ 21:369–376.

Hoek G, Meijer R, Scholten A, Noij D, Lebret E. 1984. The relationship between indoor nitrogen dioxide concentration levels and personal exposure: A pilot study. Int Arch Occup Environ Health 55:73–78.

Houthuijs D, Dijkstra L, Brunekreef B, Boleij JSM. 1990. Reproducibility of personal exposure estimates for nitrogen dioxide over a two year period. Atmos Environ 24A:435–437.

Lambert WE, Samet JM, Stidley CA, Spengler JD. 1992. Classification of residential exposure to nitrogen dioxide. Atmos Environ 26A:2185–2192.

Leaderer BP. 1982. Air pollutant emissions from kerosene space heaters. Science 218:1113–1115.

Leaderer BP, Zagraniski RT, Berwick M, Stolwijk JAJ. 1986. Assessment of exposure to indoor air contaminants from combustion sources: Methodology and application. Am J Epidemiol 124:275–289.

Lebret E. 1985. Air Pollution in Dutch Homes: An Exploratory Study in Environmental Epidemiology. Department of Environmental and Tropical Health, Wageningen Agricultural University, Wageningen, The Netherlands.

Marbury MC, Harlos DP, Samet JM, Spengler JD. 1988. Indoor residential NO_2 concentrations in Albuquerque, NM. J Air Pollut Control Assoc 38:392–398.

McCarthy SM, Yarmac RF, Yocom JE. 1987. Indoor nitrogen dioxide exposure: The contribution from unvented gas space heaters. In: Indoor Air '87, Vol. I, Volatile Organic Compounds, Combustion Gases, Particles and Fibres, Microbiological Agents (Seifert B, Esdorn J, Fischer M, Rüden H, Wegner J, eds.). Institute for Water, Soil, and Hygiene, Berlin, Germany.

Melia RJ, Florey C du V, Morris RW, Goldstein BD, John HH,

Clark D, Craighead IB, MacKinlay JC. 1982. Childhood respiratory illness and the home environment: II. Association between respiratory illness and nitrogen dioxide, temperature and relative humidity. Int J Epidemiol 11:164–169.

Middle Rio Grande Council of Governments. 1992. 1993 Transportation Program for the Albuquerque Area. Middle Rio Grande Council of Governments of New Mexico, Albuquerque, NM.

National Research Council, Committee on the Epidemiology of Air Pollutants. 1985. Epidemiology and Air Pollution. National Academy Press, Washington, DC.

Neas LM, Dockery DW, Ware JH, Spengler JD, Speizer FE, Ferris BG Jr. 1991. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. Am J Epidemiol 134:204–219.

Noy D, Winkes A, Willers H, Lebret E, Brunekreef B, Boleij JSM. 1986. Estimating human exposure to nitrogen dioxide. Environ Int 12:407–412.

Ozkaynak H, Ryan PB, Spengler JD, Laird NM. 1986. Bias due to misclassification of personal exposures in epidemiologic studies of indoor and outdoor air pollution. Environ Int 12:389–393.

Palmes ED, Gunnison AF, DiMattio J, Tomczyk C. 1976. Personal sampler for nitrogen dioxide. Am Ind Hyg Assoc J 37:570–577.

Parkhurst WJ, Dumyahn T, Cropp JW. 1990. Intervention study to reduce nitrogen dioxide in a Chattanooga, Tennessee, public housing development. In: Combustion Processes and the Quality of the Indoor Environment (Harper JP, ed.) pp. 74–84. Air and Waste Management Association, Pittsburgh, PA.

Quackenboss JJ, Spengler JD, Kanarek MS, Letz R, Duffy CP. 1986. Personal exposure to nitrogen dioxide: Relationship to indoor/outdoor air quality and activity patterns. Environ Sci Technol 120:775–783.

Robinson J. 1988. Time-diary research and human exposure assessment: Some methodological considerations. Atmos Environ 22:2085–2092.

Ryan PB, Soczek ML, Spengler JD, Billick I. 1988a. The Boston residential NO_2 characterization study: I. Preliminary evaluation of survey methodology. J Air Pollut Control Assoc 38:22–27.

Ryan PB, Soczek ML, Treitman RD, Spengler JD. 1988b. The Boston residential NO_2 characterization study: II. Survey methodology and population concentration estimates. Atmos Environ 22:2115–2125.

Ryan PB, Spengler JD, Schwab M, Scozek ML. 1990. Nitrogen dioxide exposure studies: I. The Boston personal monitoring study. In: Proceedings of the Environmental Protection Agency/Air and Waste Management Association Symposium on Total Exposure Assessment Methodology, pp. 38–65. Air and Waste Management Association, Pittsburgh, PA.

Samet JM, Lambert WE, Skipper BJ, Cushing AH, McLaren LC, Schwab M, Spengler JD. 1992. A study of respiratory illnesses in infants and nitrogen dioxide exposure. Arch Environ Health 47:57–63.

Samet JM, Lambert WE, Skipper BJ, Hunt WC, Cushing AH, Young SA, McLaren LC, Schwab M, Spengler JD. 1993. Nitrogen Dioxide and Respiratory Infection in Children, Part I: Health Outcomes. Research Report Number 58. Health Effects Institute, Cambridge, MA.

Samet JM, Marbury MC, Spengler JD. 1987. Health effects and sources of indoor air pollution, Part I. Am Rev Respir Dis 136:1486–1508.

Samet JM, Spengler JD. 1989. Nitrogen Dioxide and Respiratory Infection: Pilot Investigations. Research Report Number 28. Health Effects Institute, Cambridge, MA.

Samet JM, Utell MJ. 1990. The risk of nitrogen dioxide: What have we learned from epidemiological and clinical studies? Toxicol Ind Health 6:247–262.

Schwab M, Spengler JD, Ryan PB, Billick IH. 1990. Describing exposure to NO_2: Data from personal monitoring in Los Angeles. In: Indoor Air '90, Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Vol. 2, Characteristics of Indoor Air (Akland G, Spengler J, eds.) pp. 589–594. International Conference on Indoor Air and Climate, Ottawa, Canada.

Shy CM, Kleinbaum DG, Morgenstern H. 1978. The effect of misclassification of exposure status in epidemiological studies of air pollution health effects. Bull NY Acad Med 54:1155–1165.

Spengler JD, Duffy CP, Letz R, Tibbitts TW, Ferris BG Jr. 1983. Nitrogen dioxide inside and outside 137 homes and implications for ambient air quality standards and health effects research. Environ Sci Technol 17:164–168.

Spengler JD, Ryan PB, Schwab M, Colome S, Wilson AL, Billick I, Becker E. 1990. An overview of the Los Angeles personal monitoring study. In: Proceedings of the Environ-

mental Protection Agency/Air and Waste Management Association Symposium on Total Exposure Assessment Methodology, pp. 66–85. Air and Waste Management Association, Pittsburgh, PA.

Sterling TD, Dimich H, Kobayashi D. 1981. Use of gas ranges for cooking and heating in urban dwellings. J Air Pollut Control Assoc 32:162–165.

Tukey JW. 1977. Exploratory Data Analysis. Addison-Wesley, Reading, MA.

U.S. Environmental Protection Agency. 1990. National Air Quality and Emissions Trends Report, 1988. EPA-450/4–90/002. Office of Air Quality Planning and Standards, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1991. National Air Quality and Emissions Trends Report, 1989. EPA-450/4–91/003. Office of Air Quality Planning and Standards, Research Triangle Park, NC.

Wiley JA. 1991. Study of Children's Activity Patterns. Final Report. Contract No. A733–149. Research Division, California Air Resources Board, Sacramento, CA.

ABOUT THE AUTHORS

William E. Lambert, the Project Coordinator for these studies, is Research Assistant Professor in the Department of Family and Community Medicine. He is completing his Ph.D. at the University of California, Irvine, in the Department of Environmental Health and Design, School of Social Ecology. His research interests have focused on assessment of exposure to air pollutants and the measurement of health effects in the community setting.

Jonathan M. Samet, M.D., the Principal Investigator for these studies, is Professor of Medicine and Chief of the Pulmonary and Critical Care Division at the University of New Mexico Hospital, and is the Director of Epidemiology at the New Mexico Tumor Registry. He received his M.D. degree from the University of Rochester School of Medicine and Dentistry, and received clinical training in internal medicine and the subspecialty of pulmonary diseases. He completed a three-year fellowship in clinical epidemiology at the Channing Laboratory, Harvard Medical School, and has an M.S. in epidemiology from the Harvard School of Public Health. His research interests focus on environmental and occupational epidemiology and the effects of chemical and radioactive agents on the lung.

William C. Hunt, M.A., is a statistician and programmer with the New Mexico Tumor Registry. He received his M.A. from the Department of Mathematics and Statistics at the University of New Mexico.

Betty J. Skipper, Ph.D., the Project Biostatistician, has also been affiliated with the Study since the earliest stages of its inception and design. She is Professor of Family and Community Medicine at the University of New Mexico School of Medicine. She received her Ph.D. degree in biostatistics from Case Western Reserve University.

Margo Schwab, Ph.D., coordinated the handling of the NO_2 data at the Harvard School of Public Health. This work included developing the quality control program, and the statistical analyses of household and seasonal factors determining NO_2 concentrations in homes. She received her Ph.D. degree in Geography from Clark University. Her research interests include human exposure assessment and time-activity patterns of populations. She is currently with ManTech Environmental, Inc., Research Triangle Park, NC.

Jack Spengler, Ph.D., the Principal Investigator for the Harvard component of the study, is Professor of Environmental Health Sciences at the Harvard School of Public Health. He received a Ph.D. in Atmospheric Sciences from the State University of New York at Albany, and an M.S. in Environmental Health Sciences from the Harvard School of Public Health. His research has focused on the measurement of air pollutants inside homes and on the assessment of personal exposure to air pollutants.

PUBLICATIONS RESULTING FROM THIS RESEARCH

The following list includes only those papers that have been submitted for publication at the time this report went to press. Please call or write to the Health Effects Institute for an updated list.

Samet JM, Utell MJ. 1990. The risk of nitrogen dioxide: What have we learned from epidemiological and clinical studies? Toxicol Ind Health 6:247–262.

Samet JM, Lambert WE. 1991. Epidemiologic approaches for assessing health risks from complex mixtures in indoor air. Environ Health Perspect 95:71–74.

Samet JM, Utell MJ. 1991. The environment and the lung: Changing perspectives. JAMA 226:670–675.

Lambert WE, Samet JM, Dockery DW. 1992. Community air pollution. In: Environmental and Occupational Health, 2nd Ed. (Rom WN, ed.). Little, Brown & Co., Boston, MA.

Lambert WE, Samet JM, Stidley CA, Spengler JD. 1992. Classification of exposure to residential nitrogen dioxide exposure. Atmos Environ 26A:2185–2192.

Samet JM, Lambert WE, Skipper BJ, Cushing AH, McLaren LC, Schwab M, Spengler JD. 1992. A study of respiratory illnesses in infants and nitrogen dioxide exposure. Arch Environ Health 47:57–63.

Spengler JD, Brauer M, Samet JM, Lambert WE. 1993. Nitrous acid in Albuquerque, New Mexico, homes. Environ Sci Technol (in press).

ABBREVIATIONS

CI	confidence interval
NAAQS	National Ambient Air Quality Standard
NO_2	nitrogen dioxide
ppb	parts per billion

INTRODUCTION

Respiratory infections are the most common type of infections in developed countries. In older children and most adults, mortality rates from most types of respiratory infection are generally low; the most serious concerns relate to the costs of treatment and lost income. However, respiratory infections, especially infections of the lower respiratory tract, can have serious consequences for particularly susceptible groups, especially infants and the elderly. Clinical studies suggest that host factors and environmental factors act together to increase the risk of developing respiratory infections. From the public health perspective, it is important to determine whether air pollutants are among the environmental factors that increase susceptibility to respiratory infections. Some epidemiologic studies suggest that nitrogen dioxide, a component of outdoor and indoor air, is one such environmental risk factor; the National Ambient Air Quality Standards (NAAQS) are based, in part, on these findings.

The Clean Air Act establishes a regulatory framework for defining and attaining air quality in the United States. The Clean Air Act Amendments of 1970 require the U.S. Environmental Protection Agency (EPA) to establish primary standards for air pollutants based on health effects and at levels "requisite to protect the public health . . . allowing an adequate margin of safety." The legislative history of the act makes it clear that in setting the ambient air quality standards, the EPA is required to consider the health of particularly sensitive subgroups of the population.

The current primary NAAQS for nitrogen dioxide is 53 parts per billion (ppb) (100 $\mu g/m^3$), as an annual arithmetic mean concentration. Established in 1971, when there were limited data on the health effects of nitrogen dioxide, this standard was originally based on epidemiologic studies that indicated an association between elevated outdoor levels of nitrogen dioxide and respiratory illness in schoolchildren (Shy et al. 1970a,b). Although the results of these studies were later questioned because of limitations in the study design and exposure assessment (Warner and Stevens 1973; Ferris 1978), the data from clinical and toxicological studies were considered sufficiently supportive of the possible adverse health effects of nitrogen dioxide exposure to warrant retaining the standard when it was last reviewed more than 10 years ago.

At that time, it was also recognized that indoor exposures to nitrogen dioxide are often much higher than outdoor exposures. Some epidemiologic studies of children living in homes with gas stoves (a major source of nitrogen dioxide) found an association between the use of gas as a cooking or heating fuel and respiratory illness; however, in other studies, no such association was found. It was suggested that these inconsistent findings might be due, in part, to methodological limitations in many of the early studies, including inadequate sample size, misclassification of exposures and health outcomes, and failure to control for confounding variables. Although the NAAQS applies to outdoor air, the results of indoor studies often provide better information on pollutant concentrations and individual exposures than outdoor investigations. Because the determination of the NAAQS for nitrogen dioxide depends, in part, on the health risks that exposures present for respiratory disease, improved information on the relationship between indoor nitrogen dioxide and respiratory illness in children is needed to provide regulators with reliable data on which to base the nitrogen dioxide standard.

In 1983, the Health Effects Institute (HEI) initiated a multidisciplinary research program to help resolve the issue of whether or not exposure to nitrogen dioxide is a risk factor for respiratory infections. Under this program, three toxicological studies (Jakab 1988; Rose et al. 1989; Davis et al. 1991) were funded to examine the influence of short-term exposures to nitrogen dioxide on the susceptibility of mice to viral, bacterial, and mycoplasmal infections. A fourth study, a controlled clinical study, tested the effect of short-term nitrogen dioxide exposures on the response of human volunteers to an attenuated cold-adapted influenza A virus (Kulle and Clements 1988).

In that same year, HEI invited research applications for "Epidemiologic Investigations of the Effects of Automotive Emissions." Under this program, the Institute supported a retrospective assessment of data from a study of British coal miners to determine whether occupational exposures to nitrogen oxides were associated with increased susceptibility to respiratory infections (Jacobsen et al. 1988). In addition, the Health Research Committee specifically encouraged proposals for studies designed to address the limitations of previous epidemiologic investigations, namely, the documentation of nitrogen dioxide exposure levels and patterns, the consideration of confounding variables, and the identification of infectious agents. In response, Drs. Jonathan M. Samet and John D. Spengler submitted a joint proposal to test the hypothesis that exposure to nitrogen dioxide increases the occurrence of respiratory infections in infants during the first 18 months of life. The HEI Health Research Committee recommended that pilot studies be conducted in a small sample population to assess the feasibility of the proposed methods. Two pilot studies were eventually funded by HEI; the results were reviewed by the HEI Research and Review Committees and published in HEI Research Report Number 28 (Samet and Spengler 1989). The

full study began in April 1987, and the data collection phase was completed in December 1991. In addition to the usual HEI support from the EPA and the Institute's motor vehicle sponsors, the study was partially supported by a special grant to HEI from the Gas Research Institute.

This study generated data that will take many years to analyze fully. In order to expedite the review and publication of the major findings, the investigators submitted draft reports of the results concerning nitrogen dioxide and respiratory illness as soon as they had been analyzed (June 1992). Background information relevant to Parts I and II will be submitted to HEI in 1993 and will be published in later reports. This information includes data on (1) quality assurance (comparability of parental reports of respiratory illnesses with clinical diagnoses, and subject compliance with monitoring protocols); (2) effects of housing and meteorologic factors on indoor concentrations of nitrogen dioxide, and (3) frequency of infants' exposure to peak concentrations of nitrogen dioxide. This Commentary deals with the major findings as contained in the Investigators' Reports, "Nitrogen Dioxide and Respiratory Illness in Children, Part I: Health Outcomes, and Part II: Assessment of Exposure to Nitrogen Dioxide."

The following Scientific Background section provides an overview of the scientific basis for linking nitrogen dioxide exposure with an increased risk of respiratory illness and describes how research that addresses the health effects of nitrogen dioxide exposure has been used to develop ambient air quality standards. The findings of numerous epidemiological, clinical, and toxicological studies have been summarized in documents published by the EPA (1991a) and the California EPA Air Resources Board (1992a,b) and have been the subject of recent review articles (Samet et al. 1987; Graham 1990; Samet and Utell 1990; Samet 1991). Therefore, the Scientific Background section is not a comprehensive review of all the health effects data. This section discusses where nitrogen dioxide exposures occur and how they are monitored, considers the potential human health effects of exposure to nitrogen dioxide, and focuses on the epidemiologic studies that have addressed whether indoor or outdoor nitrogen dioxide exposures are associated with an increased risk of respiratory illness in children. The Regulatory Background section presents the basis for the federal and state standards for nitrogen dioxide.

SCIENTIFIC BACKGROUND

NITROGEN DIOXIDE SOURCES AND EXPOSURES

Nitrogen oxides are common outdoor and indoor air pollutants. There are a number of different oxides of nitrogen in ambient air, the most abundant being nitric oxide (NO) and nitrogen dioxide (NO_2). These compounds are important because they participate in a series of photochemical reactions that affect ozone production, and because of the potential health effects of oxides of nitrogen themselves. Collectively, the two most abundant nitrogen oxides are referred to as NO_x, the sum of nitric oxide and nitrogen dioxide. In the past, more attention has been paid to nitrogen dioxide than nitric oxide because some of the early laboratory animal studies indicated that nitrogen dioxide was more toxic than nitric oxide. However, it is now known that nitric oxide, which has a free radical structure, is a potent regulator of diverse biological functions in the human brain, nerves, lungs, cardiovascular system, and immune system (reviewed in Science 1992). Recently, Rossaint and coworkers (1993) reported that inhaling 5,000 to 20,000 ppb nitric oxide reduced pulmonary hypertension and improved gas exchange in patients with adult respiratory distress syndrome. These findings suggest that, in the future, more attention may need to be paid to the possible deleterious effects of nitric oxide and other oxides of nitrogen.

Nitrogen oxides are products of high-temperature combustion. During the combustion process, nitrogen in the air combines with oxygen to form nitric oxide, which is emitted into the surrounding air or discharged in engine exhaust. In the atmosphere, nitric oxide is converted to nitrogen dioxide by reactions involving ozone and organic gases (National Research Council 1991b). Motor vehicles are responsible for approximately 30% of the human-made outdoor nitrogen oxides; power plants and industrial sources are also major contributors (U.S. Environmental Protection Agency 1991b). Unvented heating and cooking appliances that utilize natural gas, kerosene, coal, or wood are potential sources of indoor nitrogen oxides.

In interpreting the animal and human studies that deal with the health effects of nitrogen dioxide, it is important to understand the methods used to measure this pollutant and how the data are expressed (as an averaging time). The EPA's Aerometric Information Retrieval System and the California EPA Air Resources Board monitoring system provide the primary data base for outdoor nitrogen dioxide levels. Ambient chemiluminescent monitors measure one-hour nitrogen dioxide levels; these hourly data are then used to calculate annual average nitrogen dioxide concentrations at each monitoring site. Generally, the annual average nitrogen dioxide concentrations in the United States range from less than 5 ppb in rural areas to 42 ppb in cities; the highest annual averages (greater than 53 ppb) have been reported in Southern California (U.S. Environmental Protection Agency 1991b). Representative maximum annual average nitrogen dioxide concentrations for U.S. cities are given in Table 1. Outdoor nitrogen dioxide concentrations

Table 1. Outdoor Concentrations of Nitrogen Dioxide in Selected Metropolitan Areas in the United States, 1990[a]

City	Maximum Annual Average[b] (ppb)	Maximum Hourly Average[b] (ppb)
Albuquerque, NM	18	118
Boston, MA	32	250
Buffalo, NY	23	107
Dallas, TX	18	90
Detroit, MI	24	110
Erie, PA	15	108
Houston, TX	29	160
Los Angeles, CA	56	280
Memphis, TN	23	132
Miami, FL	16	88
New York, NY	46	213

[a] Source: U.S. Environmental Protection Agency (1991) and U.S. Environmental Protection Agency (1992a).

[b] Highest nitrogen dioxide level measured from all available sites (i.e., those monitored by the EPA that yielded valid data) within metropolitan areas in the United States having populations greater than or equal to 500,000.

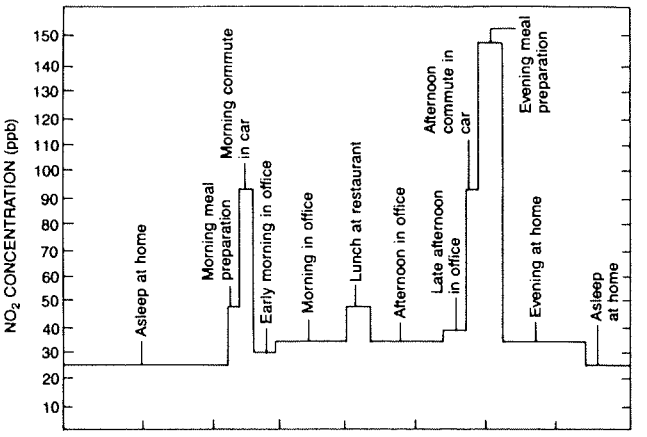


Figure 1. Example of a representative 24-hour nitrogen dioxide exposure profile and associated time-activity pattern data for one individual. Adapted with permission from K Sexton and PB Ryan, "Assessment of Human Exposure to Air Pollution: Methods, Measurements, and Models." In: *Air Pollution, the Automobile, and Public Health* (Watson AY, Bates RR, Kennedy D, eds.). Copyright 1988 by the National Academy of Sciences. Courtesy of the National Academy Press, Washington, DC.

in Albuquerque, NM, the location of the Samet study, are lower than those in many cities in the United States.

Because annual averages use an extended averaging time, they can obscure potentially important short-term fluctuations in nitrogen dioxide levels. One-hour averages provide better information about peak nitrogen dioxide exposures. For the 103 metropolitan statistical areas monitored by the EPA, the maximum one-hour nitrogen dioxide averages for 1990 ranged from 60 to 280 ppb. As can be seen in Table 1, there is a reasonably consistent relationship between the maximum annual average and the maximum hourly average outdoor nitrogen dioxide concentrations, with a few exceptions. Although the national data bases report maximum one-hour averages, it should be noted that occurrences of hourly average nitrogen dioxide concentrations greater than 100 ppb are rare; in 1990, only 5% of the reported hourly nitrogen dioxide concentrations exceeded 50 ppb (U.S. Environmental Protection Agency 1991b).

In the late 1970s, scientists began to appreciate that outdoor measurements of nitrogen dioxide underestimated actual human exposures because people spend more time indoors than outdoors (Sexton and Ryan 1988). Combustion appliances, such as gas stoves, gas heaters, furnaces, and kerosene heaters contribute to indoor nitrogen dioxide levels, which are often higher than outdoor concentrations and vary markedly over the course of a day. The contribution of indoor and outdoor nitrogen dioxide sources and the variable nature of nitrogen dioxide exposure patterns are shown in Figure 1. This figure illustrates an important point about personal nitrogen dioxide exposures, that is, in a typical day, people are exposed to background concentrations of nitrogen dioxide (10 to 30 ppb) on which short-term peaks are imposed (ranging from 20 to 145 ppb in this example). These short-term peak exposures can occur indoors, from unvented gas ranges during meal preparation, or outdoors, in urban street canyons, near highways, and in the vicinity of power plants.

Indoor nitrogen dioxide concentrations are usually measured by simple passive monitors, such as Palmes tubes, because the active chemiluminescent monitors that are used outdoors are too cumbersome and expensive for routine indoor use (Palmes et al. 1976). Passive monitors, which are less sensitive than active monitors, measure the integrated concentrations of nitrogen dioxide over intervals of one day to several weeks. The Palmes tube operates by allowing the air sample to diffuse down a tube of known length and capturing nitrogen dioxide and nitric oxide on specially coated grids. After a predetermined interval to allow sufficient exposure time, the grids are removed from the tube, the reaction product is extracted by a solvent, and its concentration is determined by a colorimetric reaction. The detection and sensitivity limits of the Palmes tubes require that samples be collected over periods ranging from several days to weeks. Thus, the Palmes tubes cannot provide information on short-term nitrogen dioxide exposures, particularly those that are on the order of minutes to hours. These so-called "peak exposures" may be one to two orders of magnitude greater than longer term average nitrogen dioxide exposures integrated over one to two weeks.

Palmes tubes have been used extensively to obtain information on indoor nitrogen dioxide levels in residential set-

tings. Data from several studies of indoor nitrogen dioxide concentrations during the winter months are given in Table 2. This table illustrates the importance of indoor nitrogen dioxide exposures in determining total exposure to this pollutant. In the winter, average indoor concentrations of nitrogen dioxide are often two to four times higher than outdoor levels, especially in locations near a gas stove or other sources of nitrogen dioxide emissions. Although bedroom nitrogen dioxide levels are generally not as high as those in the kitchen or living room, they are important in determining total exposure, especially for infants who spend most of their time in their bedrooms. Kerosene and gas space heaters are also important sources of nitrogen dioxide. Some of the highest indoor nitrogen dioxide levels have been reported in homes with unvented kerosene heaters (greater than 45 ppb) (Leaderer et al. 1986) or unvented gas space heaters (greater than 500 ppb) (Ryan et al. 1989) as the primary heating source.

Little is known about nitrogen dioxide levels in indoor environments other than homes. However, accidental releases of nitrogen dioxide can occur in a variety of settings, such as factories, missile sites, and hockey rinks (Yockey et al. 1980; Hedberg et al. 1989; Meulenbelt and Sangster 1990). Automobile interiors are now recognized as a potentially important source of exposure to nitrogen dioxide and other air pollutants (Baker et al. 1990).

HEALTH EFFECTS OF NITROGEN DIOXIDE

Clinical and Toxicological Studies

Nitrogen dioxide is called an oxidant gas because it acts as an oxidizing agent that attracts electrons from other molecules within tissues and cells. When high concentrations are inhaled, nitrogen dioxide is toxic, and sometimes lethal. Nitrogen dioxide intoxication was first recognized as an occupational hazard in the late 1940s and was given the name "silo-fillers disease" because the syndrome was reported in farmers exposed to high levels of nitrogen dioxide from fermenting silage (Lowry and Schuman 1956). The effects of acute exposure to nitrogen dioxide depend on the concentration of the gas and the duration of exposure. Short-term exposures to extremely high concentrations of nitrogen dioxide (in excess of 50,000 to 100,000 ppb) cause severe damage to lung tissue and can lead to fatal pulmonary edema (Meulenbelt and Sangster 1990). The consequences of inhaling nitrogen dioxide at concentrations that occur in typical indoor and outdoor settings (10 to 200 ppb) or even in the high ambient exposure range (200 to 1,000 ppb) have been more difficult to characterize.

Clinical studies using controlled nitrogen dioxide exposures have yielded conflicting results. Some studies have reported an increase in specific airway resistance and airway responsiveness in human subjects following short-term exposures (0.5 to 3 hours) to concentrations of nitrogen dioxide greater than 1,000 ppb (Linn et al. 1985; Kulle and Clements 1988; Mohsenin 1988). Short-term exposures of healthy subjects to nitrogen dioxide concentrations less than 1,000 ppb have not produced consistent effects on lung function or airway reactivity; studies in subjects with asthma have also produced equivocal findings. Some studies of subjects with asthma have shown enhanced airway responsiveness of subjects challenged with a bronchoconstrictor after a short-term exposure to nitrogen dioxide (100 to 1,000 ppb) (Orehek et al. 1976; Bylin et al. 1985; Bauer et al. 1986; Mohsenin 1987). However, the majority of

Table 2. Representative Nitrogen Dioxide Concentrations in Homes with Indoor Sources of Nitrogen Dioxide

Location	Number of Homes	Average NO_2 in Winter (ppb)			Reference
		Outdoor	Kitchen	Bedroom	
Albuquerque, NM[a]	1,205	15	34	21	Lambert et al. 1993
Boston, MA[a]	298	22	39	26	Ryan et al. 1988
California[b] (mobile homes)	231	22	28	20	Petreas et al. 1988
Kingston, TN[b,c]	91	15	55	43	Butler et al. 1990
Middlesbrough, United Kingdom[b]	428	19	112	31	Goldstein et al. 1979
Portage, WI[b]	34	8	37	16	Quackenboss et al. 1986
Portage, WI[b,c]	110	10	27	16	Butler et al. 1990
Southern CA[b]	141	55	29–54	28–37	Wilson et al. 1986

[a] Two-week averages.

[b] One-week averages.

[c] Six Cities study.

studies of subjects with asthma have failed to demonstrate a consistent effect of nitrogen dioxide (100 to 500 ppb) on either airway reactivity or lung function (Hazucha et al. 1982; Bylin et al. 1985; Koenig et al. 1985, 1987; Utell 1989). It has been suggested that a subgroup of individuals with asthma may be sensitive to nitrogen dioxide, but no study to date has been large enough to have adequate statistical power to test this hypothesis (Samet and Utell 1990).

In animals, long-term exposures to concentrations of nitrogen dioxide in excess of 1,000 ppb result in permanent damage to the epithelium in the centriacinar region (the junction of the conducting airways and the gas exchange region) of the lung. At lower concentrations (approximately 500 ppb), the morphologic effects are subtle and often reversible (Kubota et al. 1987). Nitrogen dioxide exposure also has little effect on the pulmonary function of rodents (Mauderly et al. 1987; Miller et al. 1987). In the few animal studies that have been conducted at nitrogen dioxide levels less than 500 ppb, no morphological effects have been demonstrated, even after prolonged continuous exposure (Kubota et al. 1987). In a large study, chronic exposure of rats to a regimen of 500 ppb nitrogen dioxide with daily spikes of 1,500 ppb produced few changes in pulmonary function; those that did occur were small and were observed after 78 weeks of exposure (Tepper et al. 1993).

There is, however, a large body of toxicological data suggesting that exposure to moderately high concentrations of nitrogen dioxide adversely affects some lung components that are important in resisting and controlling infectious microorganisms. However, there is a large degree of interspecies variability in this response (reviewed by Pennington 1988; Samet and Utell 1990). In laboratory animals, exposure to nitrogen dioxide (1,000 to 10,000 ppb) caused structural alterations in the ciliated cells that line the airways (Azoulay-Dupuis et al. 1983; Rombout et al. 1986) and reduced the mobility and phagocytic capacity of the alveolar macrophages (Acton and Myrvik 1972; Schlesinger 1987). Because these cellular and noncellular defense mechanisms represent the first line of pulmonary host defense, impairing these critical functions might extend the residence times of inhaled microorganisms on the alveolar epithelium and increase the severity of an infection.

Animal infectivity models, which combine the inhalation of nitrogen dioxide with exposure to an aerosol of viable respiratory pathogens, have been used extensively to study whether nitrogen dioxide–induced alterations in lung defense mechanisms result in increased susceptibility to experimental infections. Such studies have consistently shown increased mortality in animals exposed to high concentrations of nitrogen dioxide and then challenged with *Streptococcus* species (Goldstein et al. 1973; Miller et al. 1987). In other experiments with less virulent pathogens, HEI-funded investigators found that exposure to nitrogen dioxide decreased the intrapulmonary killing of *Staphylococcus aureus* (Jakab 1988) and *Mycoplasma pulmonis* (Parker et al. 1989; Davis et al. 1991). The relevance to humans of challenging animals with classical bacteria is not clear because viruses and *Mycoplasma pneumoniae* cause most lower respiratory infections in individuals living in developed countries (Denny and Clyde 1986; Graham 1990). The findings of Rose and coworkers (1989), who reported that mice exposed to 5,000 or 10,000 ppb nitrogen dioxide are more susceptible to infections with murine cytomegalovirus than unexposed animals, indicate that antiviral responses may also be compromised by nitrogen dioxide exposure. In experiments in which mechanisms of the nitrogen dioxide–induced damage to pulmonary defenses have been explored, it has generally been found that the phagocytic activity (Rose et al. 1989) and killing capacity (Jakab 1988; Davis et al. 1991) of the alveolar macrophages have been impaired.

Another observation made in animals that may have relevance to humans is that the adverse effects of nitrogen dioxide on lung antibacterial activity occurred at lower concentrations when the exposure to the irritant gas followed bacterial challenge, rather than when it preceded the challenge (Jakab 1988). However, one of the main limitations associated with these findings and those discussed above is the high concentration of nitrogen dioxide required to produce an effect in the animal infectivity model. The lowest nitrogen dioxide concentrations that produced effects in mice (2,000 ppb for acute exposures and 500 ppb for continuous exposure) are one to two orders of magnitude higher than typical indoor or outdoor nitrogen dioxide levels.

The mouse infectivity model has also been used to investigate the influence of the nitrogen dioxide exposure patterns on the outcome of an experimental infection. People are not continuously exposed to fixed concentrations of this pollutant; rather, gradual diurnal increases and sharp peaks (in street canyons or from gas appliances) are superimposed on low-level baseline concentrations (see Figure 1). In an attempt to mimic human nitrogen dioxide exposures, researchers have developed exposure protocols that include short-term peaks of nitrogen dioxide superimposed on continuous low-level background concentrations. Such studies suggest that short-term exposures to peak nitrogen dioxide levels have more influence on the outcome of a streptococcal infection in mice than low-level chronic exposures (Gardner et al. 1979; Graham et al. 1987; Miller et al. 1987). However, because the animal experiments involved nitrogen dioxide exposure concentrations (one year of continuous exposure to baseline levels of 200 ppb nitrogen dioxide with two daily peaks of 800 ppb) that were at least an order

of magnitude higher than typical human exposures (Miller et al. 1987), the relevance of these findings to humans is unclear.

There have been limited attempts to study the effects of nitrogen dioxide on susceptibility to infection in controlled clinical studies. Kulle and Clements (1988) exposed human subjects to either air or 1,000, 2,000, or 3,000 ppb nitrogen dioxide (two hours a day for three days). On the second day, the subjects were also exposed intranasally to an attenuated cold-adapted influenza A virus. These nitrogen dioxide exposures did not alter the rates of infection; however, the negative findings may have been due to the fact that, because of safety considerations, a highly attenuated, low-virulence virus was used (Kulle and Clements 1988; Goings et al. 1989). Recently, Utell and coworkers (1991) took another approach for studying the problem in humans. They used lavage procedures to isolate alveolar macrophages and other white blood cells from the lungs of individuals exposed to nitrogen dioxide. They then examined the ability of these cells to inactivate the influenza virus in vitro. Although the findings were not definitive, they illustrate the potential of the bronchoalveolar lavage technique to examine the effects of NO_2 exposure on pulmonary defense mechanisms in human subjects.

Epidemiologic Studies

The air pollution disasters that occurred in the United States and Europe during the middle decades of this century led to an increase in deaths, largely as a result of respiratory and cardiovascular diseases (Graham 1990). These findings stimulated further research on the health effects of air pollution, with the focus shifting from the relationship between mortality and acute air pollution episodes to morbidity and chronic air pollution scenarios (Graham 1990). Although numerous epidemiologic studies have examined the relationship between chronic exposure to nitrogen dioxide, from either outdoor or indoor sources, and respiratory illness in children, the results are inconsistent. This section will focus on some of the design considerations that have limited interpretation of the epidemiologic data, using representative studies as examples.

Many epidemiologic studies of the health effects of outdoor exposures to nitrogen dioxide have been conducted in areas of high air pollution in the United States, Europe, and Asia, where nitrogen dioxide is but one component of a complex pollutant mixture. Among the earliest studies of this type were those conducted in Chattanooga, TN, in the vicinity of a large trinitrotoluene plant. The original observations indicated an association between elevated ambient nitrogen dioxide levels and the incidence of respiratory disease in school-aged children (Shy et al. 1970a,b; Pearlman et al. 1971). However, the pollution measurements that were made at that time did not distinguish between nitrogen dioxide and other acidic gases such as nitric acid, leading some workers to question whether the observed effects were due to nitrogen dioxide (Warner and Stevens 1973). More recently, investigators in the United States (Dockery et al. 1989), Finland (Ponka 1990), Japan (Kagamimori et al. 1986), Germany (Schwartz et al. 1991), and Israel (Goren and Hellman 1988) have reported a greater prevalence of respiratory illness in children living in polluted areas than those living in less polluted communities; however, nitrogen dioxide effects generally could not be separated from those of other pollutants, such as sulfur dioxide or respirable particulate matter.

Epidemiologists have long recognized that outdoor measurements provide inadequate information on total personal exposures to air pollutants (National Research Council 1991a). Because indoor nitrogen dioxide levels are often higher than outdoor levels, and because most people spend approximately 90% of their time indoors, researchers have focused their attention on the relationship between exposure to indoor nitrogen dioxide and acute respiratory illness. As illustrated in Appendix A, these studies, which primarily have been conducted with children in their home environment, have produced conflicting results. Many studies have methodologic limitations, such as small sample size, inadequate statistical power to detect small effects, misclassification of exposure or disease outcome, and failure to adjust for confounding variables.

Accurate assessment of exposure to a pollutant is central to any epidemiologic investigation and is a major limitation in the design of many epidemiologic studies of air pollution (National Academy Press 1985; Morgenstern and Thomas 1993). In the past, the methods used to classify nitrogen dioxide exposures in epidemiologic studies were quite crude; these included using the presence of a gas stove or heater as a surrogate for nitrogen dioxide exposure, classifying nitrogen dioxide exposures according to residence near a pollution source, and relying on measurements from single-site outdoor monitors. The introduction of small passive nitrogen dioxide monitors, such as the Palmes tube, and the development of techniques for monitoring microenvironments have led to improvements in the estimates of nitrogen dioxide exposures. These methods represent significant advances; however, they only provide information on average exposures for one- or two-week periods. These methods do not take into account the intermittent nature of exposures to peaks of nitrogen dioxide, which may have health significance, nor do they measure the dose of the pollutant actually absorbed or deposited in the body.

In the first studies that examined the association between indoor air pollution and respiratory illness in children,

nitrogen dioxide exposure was often estimated by questioning the parents about the type of heating or cooking fuel in the home (Melia et al. 1977, 1979; Speizer et al. 1980; Ekwo et al. 1983; Ware et al. 1984). The results of these studies are mixed. The first study of over 5,000 British schoolchildren (from 6 to 11 years of age) showed a 1.2- to 2-fold increase in the unadjusted prevalence of selected respiratory diseases and symptoms (bronchitis, cough, colds moving to the chest) in the preceding year in children living in homes with a gas stove ($p < 0.05$) (Melia et al. 1977). In a subsequent study of 4,827 children, the crude prevalence of respiratory symptoms was lower (1.0- to 1.47-fold increase) (Melia et al. 1979).

In more recent studies, limited measurements of indoor nitrogen dioxide have been made. A companion study to the British investigations discussed above included single, one-week indoor nitrogen dioxide measurements taken during the winter months. This study demonstrated that in a small population of children (n = 103), the prevalence of respiratory illness in the preceding year increased with increasing bedroom levels of nitrogen dioxide (p = 0.05). The crude prevalence of respiratory illnesses was 44% in the low-range nitrogen dioxide group (0 to 19 ppb), 59% in the midrange group (20 to 39 ppb), and 71% in the high-range group (more than 40 ppb). When adjusted for age, gender, social class, and presence of cigarette smoking, the p value was 0.10. There was no association of the prevalence of respiratory illnesses with kitchen nitrogen dioxide levels (n = 428) (Florey et al. 1979; Goldstein et al. 1979).

Three cross-sectional analyses from cohort studies in the United States, one of 1,355 schoolchildren in Iowa (6 to 12 years of age) (Ekwo et al. 1983), the other two of more than 8,800 schoolchildren in six cities in the United States (Speizer et al. 1980; Ware et al. 1984), found no significant association of respiratory illness in the preceding year with the presence of gas stoves in the homes. However, in the Six Cities cohort, parental recall of the incidence of respiratory illnesses prior to two years of age indicated that these episodes were slightly, but significantly, higher in subjects living in homes with gas stoves (Speizer et al. 1980; Ware et al. 1984; Dockery et al. 1989). Later, a logistic regression analysis was performed for 1,567 children (7 to 11 years of age) selected from the Six Cities cohort (for whose homes one to four measurements of indoor nitrogen dioxide concentrations were available). This analysis showed a 1.4-fold increase in the cumulative incidence of selected lower respiratory symptoms in the preceding year (odds ratio = 1.4; 95% CI = 1.1, 1.7) when the data were expressed as the change in symptom rate associated with a 15-ppb increase in annual indoor nitrogen dioxide levels (Neas et al. 1991).

Weekly indoor and outdoor nitrogen dioxide measurements also were made in a six-week study of Swiss schoolchildren (0 to 5 years of age). The first cross-sectional study found a significant relationship between outdoor, but not indoor, nitrogen dioxide levels and the prevalence of respiratory symptoms (Braun-Fahrländer et al. 1989; Rutishauser et al. 1990a,b). (Approximately 30% of the study population lived in homes with gas stoves; thus, the outdoor nitrogen dioxide concentrations were higher than those measured indoors.) A second study, which included outdoor measurements of total suspended particles and sulfur dioxide, also found no relationship between indoor nitrogen dioxide levels and either the incidence (relative risk = 1.03; 95% CI = 0.89, 1.18) or duration (relative duration = 1.0; 95% CI = 0.95, 1.16) of upper respiratory illness (Braun-Fahrländer et al. 1992). There was some indication that outdoor nitrogen dioxide exposures were associated with symptom duration; however, the significance and magnitude of the effect decreased when levels of total suspended particulate matter were included in the regression model. In this study, outdoor total suspended particle levels were more significant predictors of the incidence and duration of respiratory symptoms than outdoor nitrogen dioxide.

A second limitation of many studies that examined the association between nitrogen dioxide and respiratory illness is the potential for misclassification of the disease outcomes. Clinical examination combined with microbiological testing is the most sensitive and accurate method for diagnosing respiratory infections. Because such methods are expensive and time-consuming, their suitability for large-scale community studies is limited. For this reason, many investigators have relied on retrospective determination of illness, most frequently with a self-administered parental questionnaire regarding the frequency of respiratory symptoms in the preceding year (Melia et al. 1977, 1979; Florey et al. 1979; Speizer et al. 1980; Ware et al. 1984; Dijkstra et al. 1990; Neas et al. 1991) or during the first year or two of life (Speizer et al. 1980; Ware et al. 1984). Such questionnaires are susceptible to many sources of error, such as recall bias, random error introduced by poor recall (for example, asking parents of schoolchildren to recall illnesses during infancy), and imprecise interpretation of medical terminology. Some investigators have focused on hospitalization for respiratory illness, an outcome that is less subject to poor recall, and have found an association with the presence of gas stoves in a population of American children (odds ratio = 2.4) (Ekwo et al. 1983), but not in a population of Scottish children (Ogston et al. 1985). Methods to improve the accuracy of disease assessment include the use of daily symptom diaries with a small population of Los Angeles nurses (Hammer et al. 1974; Schwartz et al. 1988; Schwartz and Zeger 1990), with residents of Tucson, AZ (Lebowitz et al. 1985), and with Swiss schoolchildren

(Braun-Fahrländer et al. 1989, 1992; Rutishauser et al. 1990a,b). The presence of a respiratory infection has not been routinely documented in most epidemiologic studies of air pollution either by clinical examination or by isolation of the infectious agent.

Assessing the incidence or severity of acute respiratory infections is difficult because the clinical classification criteria are somewhat arbitrary. Although lung function can be measured in adults and older children using spirometry and standardized procedures (American Thoracic Society 1991), there is no standard protocol for measuring respiratory illness, and no established definition of what constitutes a respiratory infection in the absence of viral or bacterial cultures. The term "respiratory illness," as it has been used in epidemiologic studies, actually encompasses a variety of clinical entities that can be broadly classified into upper respiratory tract and lower respiratory tract symptoms and diseases. Upper respiratory illnesses, such as rhinitis or nasopharyngitis, are more common and less severe than those that occur in the lower respiratory tract. In general, the clinical literature has considered four syndromes as representative of lower respiratory illness: pneumonia, bronchiolitis, bronchitis, and croup (Denny and Clyde 1986). However, as Samet points out in the accompanying report, the definition of these symptoms depends on the physician who is making the diagnosis. Some clinicians suggest that the definition of lower respiratory involvement be limited to those subjects who have signs and symptoms that are most likely attributable to the lower respiratory tract. These include pneumonia (especially if ascertained by chest films), wheezing, and laryngotracheobronchitis or croup (stridor is almost invariably present in this case). A problem arises with cough, which may or may not be associated with lower respiratory tract involvement. For example, irritation of the upper airways may be associated with cough without significant involvement of the lower respiratory tract. Cough is also a common symptom of asthma, and, in the young child, it is difficult to distinguish asthma from repeated lower respiratory tract infections and "wheezy bronchitis." As Appendix A indicates, the clinical end points used in studies of air pollution and respiratory illness vary widely among studies. One of the most frequently used end points, cough, although often interpreted as a symptom of a lower respiratory infection, can be associated with either upper or lower respiratory illnesses.

In summary, despite intensive research over the last two decades, the relationship between indoor exposures to nitrogen dioxide and respiratory illness is still not known. Although some studies have shown a small, but significant increase in respiratory illness in children exposed to an indoor source of nitrogen dioxide (Melia et al. 1977, 1979; Florey et al. 1979; Neas et al. 1991), the results of other studies have shown either no effect (Keller et al. 1979a,b; Melia et al. 1982; Schenker et al. 1983; Djikstra et al. 1990), a marginal or nonsignificant association (Ware et al. 1984), or equivocal results (Braun-Fahrländer et al. 1989, 1992).

Recently, Hasselblad and colleagues (1992) conducted a meta-analysis of the major studies of respiratory illness in children (0 to 12 years of age) exposed to nitrogen dioxide in their homes. As part of their analysis, the authors made a number of assumptions, namely that the end point being compared, lower respiratory symptoms, was common to all studies, that results from different studies were not correlated, and that each study controlled for key covariates, or that proper adjustments for the covariates were made. Although the end points that were selected for comparison are indicators of respiratory illness, the examples in Appendix A illustrate that they include a mixture of symptoms and diseases (cough, colds going to chest, chronic wheezing and cough, bronchitis, chest cough with phlegm, episodes of respiratory illness, and various indexes of combined symptoms) that are not all necessarily specific for lower respiratory tract disease. For studies in which odds ratios were not published, the authors reanalyzed the data using a multiple-logistic model to compute an odds ratio and 95% confidence intervals for the effects of nitrogen dioxide exposure. Because the nitrogen dioxide exposure levels differed among studies, and nitrogen dioxide measurements were not made in all investigations, an increase of 30 $\mu g/m^3$ (approximately 15.0 ppb) nitrogen dioxide (as determined by Neas et al. 1991) in homes with gas stoves was used as the standard increase. The conclusion of the analysis was that the 11 studies, when combined, yielded an estimated odds ratio of 1.18 (95% CI, ranging from 1.08, 1.29 to 1.11, 1.25, depending on the statistical model used) for a 30-$\mu g/m^3$ increase in nitrogen dioxide. This value is commonly interpreted as indicating an increase of approximately 18% in the odds of respiratory illness in children exposed for extended periods to an additional 15.0 ppb nitrogen dioxide.

A limited number of studies have addressed specifically the influence of exposure to emissions from gas stoves on respiratory disease in infants. This population presents a particularly high risk for respiratory tract infections (Denny and Clyde 1986; Wright et al. 1989; Holberg et al. 1991). As a part of a study of British children, trained field workers interviewed the mothers of 390 one-year-old infants and tabulated information on respiratory symptoms and cooking fuel (Melia et al. 1983). In this small study, no relationship was found between the presence of gas stoves and the prevalence of symptoms recalled by the mother or the frequency of respiratory symptoms recorded by a physician. Ogston and coworkers (1985) examined respiratory illnesses in 1,565 infants in Scotland in two ways: by monitoring hospital records for admission for respiratory illness and by

having a health professional interview mothers when the children were one year of age and asking them to recall the child's illnesses during the preceding year. A small, nonsignificant increase ($p>0.10$) was found in both outcomes in infants living in homes with gas stoves. As part of a survey of 1,355 Iowa schoolchildren, parents were asked whether their children had been hospitalized before the age of two years with chest illnesses (Ekwo et al. 1983). The investigators reported a 2.4-fold increase ($p<0.001$) in hospitalization for chest illnesses during infancy in children living in homes with gas stoves. The parental questionnaire used in the Six Cities study of schoolchildren included a question about the history of doctor-diagnosed respiratory illness before two years of age (Ware et al. 1984). In this population of 9,000 white children, parental reports of respiratory illness during the first two years of life were slightly higher (odds ratio 1.13; 95% CI 0.99, 1.28; p = 0.07) for children living in homes with gas stoves. Margolis and coworkers (1992) examined a number of risk factors for respiratory illnesses and found no significant association of gas stoves and the relative risk (relative risk = 1.14; 95% CI 0.63, 2.04) of persistent respiratory symptoms in 393 infants living in North Carolina. In summary, only one epidemiologic study has found a strong association between living in homes with gas stoves and respiratory illness in infants under the age of two years (Ekwo et al. 1983). Two studies depended on parental recall of the health outcome four or more years after the event (Ekwo et al. 1983; Ware et al. 1984), and none of the infant studies included actual nitrogen dioxide measurements. The odds ratios and confidence intervals for the infant studies are illustrated in Figure 2.

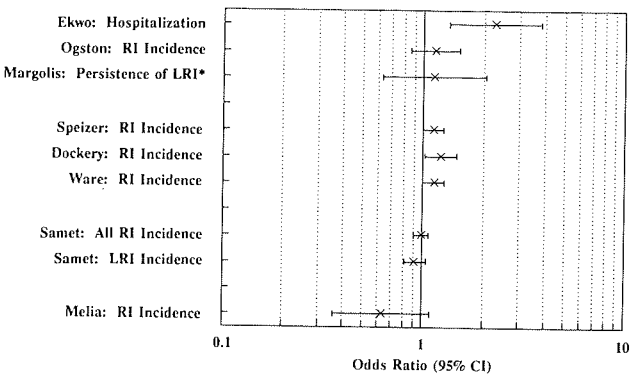


Figure 2. Odds ratios and 95% CIs for studies in infants of the association of nitrogen dioxide or gas stove exposure and respiratory illness. For the studies by Samet, Melia, Ogston, and Margolis, the subjects were infants. For the other studies, subjects were children six years of age and older whose parents were questioned about illness events during infancy. RI = respiratory illness; LRI = lower respiratory illness; * = relative risk.

REGULATORY BACKGROUND

The EPA sets standards for air pollutants under Section 202 of the Clean Air Act, as amended in 1990. The NAAQS have been established for six air pollutants: nitrogen dioxide, ozone, carbon monoxide, particulate matter, lead, and sulfur dioxide. These pollutants, which are primary and secondary emission products from transportation and industrial sources, are considered to cause health effects when people receive sufficiently high exposures. A recent survey indicates that 74 million people live in areas of the United States where at least one air quality standard, most frequently the ozone standard, is exceeded (U.S. Environmental Protection Agency 1991b). The NAAQS are set as threshold concentrations, that is, concentrations of the specific pollutant below which no adverse human health effects are expected. They are set by the EPA Administrator and are based on a detailed evaluation of the available scientific literature, with a scheduled review at five-year intervals to incorporate relevant new information.

The primary NAAQS for nitrogen dioxide is 53 ppb as an annual arithmetic mean concentration. When the primary standard was first set in 1971, it was based mainly on the findings of outdoor epidemiologic studies (Shy et al. 1970a,b; Pearlman et al. 1971) that were later found to have methodologic limitations. When the scientific basis for the nitrogen dioxide standard was reviewed in the late 1970s and early 1980s, the epidemiologic studies were considered to be inconclusive, and although the animal studies suggested an effect of nitrogen dioxide exposure on host defense mechanisms, the exposures were generally one or two orders of magnitude higher than ambient levels. Nevertheless, the Agency determined that when considered together, the animal and human data supported the theory that nitrogen dioxide exposure may increase either the frequency or the severity of respiratory infections. The EPA administrator therefore recommended that the primary nitrogen dioxide standard not be changed. He also recommended that no change be made in the form of the standard (that is, the averaging time), because the evidence for short-term effects was considered to be inadequate. As part of its mandated periodic review of the available scientific evidence, the EPA is currently reexamining the scientific literature relevant to the NAAQS for nitrogen dioxide.

Other state, national, and international organizations have reviewed the health data on nitrogen dioxide exposure and either have set or recommended different standards (Appendix B). For example, the California Air Resources Board has authority under Title 17 of the California Administrative Code to establish ambient air quality standards for air pollutants. The California standard differs from the federal standard in that it is an hourly average, rather than

an annual average. The current California nitrogen dioxide standard, which has been at the same level since 1966 and was retained when reviewed in 1992, is 250 ppb averaged over one hour. The standard was originally based on atmospheric discoloration, but is now based on human studies that are considered to suggest a potential for nitrogen dioxide to aggravate chronic respiratory disease in sensitive populations, namely people with asthma, and on some animal tests with short-term exposures (California Environmental Protection Agency Air Resources Board 1992a,b). Many regulatory agencies in Europe and Asia also favor the one-hour standard. Occupational standards, which are designed to protect workers from the adverse effects of acute exposures, are set at 1,000 ppb (Occupational Safety and Health Administration) or 5,000 ppb (National Institute of Occupational Safety and Health), using a 15-minute averaging time.

The above discussion focuses on the federal NAAQS for nitrogen dioxide, which is a health-based standard. However, it should be noted that in the future, nitrogen dioxide may be even more tightly regulated under State Implementation Plans for reducing ozone. This is because nitrogen oxides, together with volatile organic compounds, play a key role in ozone formation. In the past, ozone reduction strategies focused on controlling emissions of organic compounds. However, a recent report of the National Research Council (1991b) concluded that controlling nitrogen oxides is essential for reducing ozone levels in many regions of the United States. Because many areas do not comply with the ozone standard, and only one or two fail to meet the nitrogen dioxide standard, future controls of nitrogen oxide emissions may be based on strategies for controlling ozone rather than meeting the nitrogen dioxide NAAQS.

Determining the appropriate standards for emissions of nitrogen dioxide, ozone, and their precursors depends, in part, on an assessment of the health risks they present. Therefore, research into the health effects of oxides of nitrogen in studies such as this one is essential to the informed regulatory decision-making required by the Clean Air Act.

JUSTIFICATION FOR THE STUDY

Respiratory infections are the most common infections in people and a major cause of childhood illnesses in the United States (Denny and Clyde 1986; Taussig et al. 1989; Wright et al. 1989). Although most respiratory infections in children do not lead to immediate serious consequences, there is concern that their occurrence in infancy may be a predisposing factor for the development of chronic lung disease (Samet et al. 1983; Glezen 1989). Episodes of acute respiratory illness in the first two years of life may be associated with later manifestations of impaired lung function (Gold et al. 1989), chronic bronchitis (Barker and Osmond 1986), and reactive airway disorders (Busse 1989).

Lung injury results from the interactive effects of a number of factors, including host susceptibility, environmental factors (smoking and indoor and outdoor air pollution), social factors (socioeconomic status, race), and the frequency and severity of infections during early childhood. Well-designed epidemiologic studies, which control for misclassification effects and confounding variables, are important for determining the relative contributions of the many environmental risk factors for respiratory illness in infants.

STUDY BACKGROUND

Details on the investigators' original proposal, the preliminary pilot studies, project oversight, and the HEI review process can be found in Appendix C. Briefly, in response to a Request for Applications issued by HEI in 1983, Drs. Jonathan Samet and John Spengler submitted a proposal, entitled "Nitrogen Dioxide and Respiratory Infections in Infants," in which they proposed to test the hypothesis that exposure to nitrogen dioxide increases the frequency or severity of respiratory infections in infants during the first 18 months of life. After the investigators had demonstrated the feasibility of their approach by successfully completing two pilot studies (Samet and Spengler 1989), the Research Committee approved the full five-year study in 1987. The projected total costs for the study, which ended in December 1992, are $3.43 million dollars. The Gas Research Institute contributed one third of the research costs and provided additional administrative support. The remainder came from HEI's regular sponsors, the EPA and 28 motor vehicle and engine manufacturers. During the course of the study, the investigators received advice from the HEI Advisory Committee and outside consultants (see Appendix C). The project managers at HEI facilitated communication between the investigators, the Advisory Committee, and the consultants.

Because of the complexity of the project, the large data base, and the need to communicate rapidly the results for regulatory purposes, the findings of this study are being presented in a series of reports; the first two deal with the assessment of nitrogen dioxide exposures and the health outcomes. In June 1992, the investigators submitted the following documents to HEI:

1. Draft Investigators' Report Number 1: Nitrogen Dioxide and Respiratory Infection in Children, by JM Samet, WE Lambert, BJ Skipper, AH Cushing, WC Hunt, SA Young, LC McLaren, M Schwab, and JD Spengler.

2. Draft Investigators' Report Number 2: Characterization of Infants' Residential Exposures to Nitrogen Dioxide, by WE Lambert, JM Samet, WC Hunt, BJ Skipper, M Schwab, and JD Spengler.
3. Appendix: Comparability of Parent Reports of Respiratory Illnesses with Clinical Diagnoses in Infants (information on diagnostic criteria; not included in Parts I and II), by JM Samet, AH Cushing, WE Lambert, WC Hunt, LC McLaren, SA Young, and BJ Skipper.

Later, additional reports dealing with quality control procedures and detailed information on the nitrogen dioxide measurements will be submitted, reviewed, and published.

The two Investigators' Reports that form Part I and Part II of this document and the appendix were evaluated by a Technical Review Panel of experts in July 1992. The reports were revised by the investigators, discussed by the HEI Review Committee in November 1992, and accepted for publication at that time. The Health Review Committee then prepared this Commentary in accordance with standard HEI procedures. The Health Review Committee's Commentary is intended to place the investigators' work into a broad scientific context, to discuss the strengths and weaknesses of the study, and to address the public health significance of the study findings.

STUDY OBJECTIVES

The main objective of this study was to determine whether exposure to nitrogen dioxide increases the frequency or the duration, or both, of respiratory infections in children during the first 18 months of life. A secondary goal, which was necessary for achieving the main objective, was to provide accurate assessments of the nitrogen dioxide exposures in the study population.

STUDY DESIGN

In designing their study, the investigators sought to avoid the methodologic limitations of previous studies that examined the relationship between indoor nitrogen dioxide exposure and respiratory infections in children. Some of the key features of the study design were:

1. *Assessment of exposure.* Rather than relying on single nitrogen dioxide measurements or using information about the type of stove, the investigators repeatedly measured nitrogen dioxide levels in the subjects' homes during the entire 18-month observation period.
2. *Assessment of health outcomes.* Information about respiratory illnesses was collected prospectively rather than retrospectively. Episodes of respiratory illness were ascertained through a surveillance system using reports in parental diaries and telephone interviews at two-week intervals. These reports were validated by clinical diagnosis and viral isolation for a sample of children.
3. *Subjects.* Subjects were accrued prospectively in a systematic manner by screening deliveries of all healthy, live babies at all Albuquerque hospitals and checking eligibility criteria immediately after birth.
4. *Confounding factors.* The potential for confounding by two major determinants of respiratory infection in infants, exposure to environmental tobacco smoke and day care, was reduced by selecting only infants from homes where there were no smokers, excluding newborns whose mothers planned to use day care, and dropping subjects if they spent more than 20 hours per week in day care. Other potential confounding factors (breast feeding, atopy, family composition, ethnicity, and socioeconomic status) were controlled in the analysis. Seasonal variation and effects of gender and age of the infants were investigated in preliminary studies and accounted for in the analyses.

OVERALL DESIGN

The design was a prospective cohort study of 1,205 infants living in homes with gas or electric stoves in Albuquerque, NM. The original proposal was to recruit a population of infants from homes with gas stoves. The infants were to be stratified according to the levels of nitrogen dioxide exposure ascertained during an initial two-week observation period. Because it was uncertain whether single, two-week measurements would accurately predict long-term exposures, the strategy was changed, and subjects were recruited from households with gas or electric cooking stoves in the ratio of 4:1, without regard to the level of nitrogen dioxide exposure.

Because of the concern that short-term exposures to peaks of nitrogen dioxide may have a greater impact on host defenses than long-term exposures to low concentrations, the original plan included a nested case control study of 200 subjects in order to provide information on patterns of peak nitrogen dioxide exposures and on the importance of peak exposures in determining health outcomes. However, when preliminary experiments indicated that there were problems obtaining accurate measurements with the continuous nitrogen dioxide monitors available at that time, the Health Research Committee agreed with the investigators' recommendation that the peak exposure study be modified. During the latter phase of the study, the investigators conducted extensive validation experiments using new instru-

ments and initiated field work to compare the performance of the continuous portable monitors with the integrated nitrogen dioxide measurements from Palmes tubes located in the same place. The results of the peak nitrogen dioxide experiments will be published in a later report.

The design of the study and procedures for collecting and analyzing the data were based on results of extensive pilot studies. Indoor pollutants other than nitrogen dioxide, namely, particles, heavy metals, and formaldehyde, were measured in the pilot studies; no differences were reported in the levels of these pollutants among homes with high and low levels of nitrogen dioxide (Samet and Spengler 1989).

The study subjects were normal infants and toddlers, who have a higher risk for respiratory illness than older children (Denny and Clyde 1986; Wright et al. 1989; Holberg et al. 1991, 1993). The infants in this study were enrolled at birth and observed to the age of 18 months. Potential subjects were identified by screening deliveries of healthy infants at all Albuquerque hospitals. Ineligible infants included infants requiring intensive care, premature infants, babies with low birth weight or major congenital anomalies, and infants not residing within Metropolitan Albuquerque. The subjects' mothers had to be 18 years of age or older, English speaking, intending to care for the infant at home, and without plans to move from Albuquerque. Telephones had to be present in the household, and all members of the household had to be nonsmokers. Infants who spent more than 20 hours/week in day care, moved from Albuquerque, were exposed to cigarette smoke at home, or whose mothers failed to comply with the study procedures were dropped from the study. Details on the subject selection criteria can be found in Part I of the Investigators' Report.

EXPOSURE ASSESSMENT

Infant exposure to nitrogen dioxide was carefully monitored during the first 18 months of life. Because it was not practical to place passive samplers on the infants' clothing, measurements were obtained in the rooms of the homes where the infants were likely to spend the majority of time, namely, the child's bedroom, the living room (or activity room), and kitchen. Monitoring data were collected from January 1988 to December 1991 in 1,416 separate residences. Nitrogen dioxide concentrations were measured with Palmes tubes that were placed in the infants' bedrooms and exchanged by the parents on a two-week cycle in homes with gas stoves and on alternate two-week cycles in homes with electric stoves. During alternate months in the fall and winter, nitrogen dioxide measurements were made in the kitchens and living rooms of homes with gas stoves. Outdoor measurements of nitrogen dioxide concentrations were made at 11 ambient monitoring sites operated by the city of Albuquerque, also using two-week integrated data obtained from passive samplers.

The Air Quality Laboratory at the Harvard School of Public Health coordinated the nitrogen dioxide measurements. Palmes tubes were produced by the Air Quality Laboratory and sent to the University of New Mexico. The University of New Mexico personnel placed the first Palmes tubes in the subjects' homes and instructed the parents in the placement of subsequent tubes, tracked the nitrogen dioxide samples, and returned them to the Harvard School of Public Health for analysis. Each institution employed internal quality control procedures to assess the precision of the nitrogen dioxide measurements and compliance with monitoring protocols.

Data on factors that might influence residential nitrogen dioxide exposure, including cooking range and oven use, time infants spent in the kitchen during cooking, and time spent away from home were collected every two weeks via telephone interviews. At intervals of two months, recall interviews were conducted with the parents to characterize the time children had spent in various rooms of the house and away from home during the previous 24 hours. Time-activity patterns were assessed to the nearest 15 minutes, and recall was conducted in chronological order, hour by hour, from 5:00 a.m. on the previous day to 5:00 a.m. on the morning of the call.

HEALTH OUTCOMES

The goal of the health surveillance procedures was to reduce misclassification of health outcomes by obtaining more accurate and sensitive indicators of respiratory illness than those obtained with previous investigations. The primary tool used by the authors to ascertain the development of respiratory illnesses in infants was a surveillance system based on parental diaries of respiratory signs and symptoms. (Part I of the Investigators' Report provides a brief description of the methods used to evaluate respiratory illness. An appendix containing details of the surveillance system was made available to the Technical Review Panel and the HEI Review Committee. These data will be the subject of a future HEI Research Report.) To validate their illness classification scheme, the investigators compared the parental reports of respiratory illnesses with the clinical diagnoses of health care providers. They also performed virologic studies in a group of children who were diagnosed by a nurse practitioner as having a respiratory illness. The investigators' illness surveillance systems allowed them to examine two measures of health outcomes, incidence of respiratory illness and duration of illness for the following categories: all respiratory illnesses, all upper respiratory ill-

nesses, all lower respiratory illnesses, lower respiratory illnesses with wet cough, and lower respiratory illnesses with wheezing.

The incidence rates were based on the time at risk, which began on the third day after enrollment, continued until the child had an illness episode, and resumed on the third symptom-free day or the third day after any seven-day period during which the subject was outside the home without health surveillance. The incidence rates were calculated as the number of illness events divided by the number of days at risk.

The incidence rates of the various respiratory illnesses are presented in the Investigators' Report as annualized rates. It should be noted that these rates do not refer to the number of episodes of respiratory illnesses in a calendar year; they relate to the number of episodes in a period of 365 days at risk. Because it usually took more than a year to produce 365 days at risk, the annualized incidence rates in this report are not directly comparable to rates based on 365 consecutive days.

QUALITY ASSURANCE

Extensive internal and external quality assurance procedures were implemented. Internal procedures for the health assessment component of the study consisted of documenting all procedures, training the staff, and evaluating their performance. Quality control procedures for the nitrogen dioxide measurements are discussed in Part II of the Investigators' Report. The procedures included deploying 5% of the Palmes tubes as blanks and an additional 5% as replicates, conducting random audits to assess the parents' use of the tubes, and developing strict inclusion and exclusion criteria for the nitrogen dioxide measurements. The conduct of the study at the University of New Mexico and the Harvard School of Public Health was also monitored by an external quality assurance team from Arthur D. Little, Inc., Cambridge, MA. The quality assurance team periodically audited both institutions to assure that the investigators were adhering to the protocol and procedures for the study. The Quality Assurance Report is summarized in Appendix C of Part I of the Investigators' Report.

DATA ANALYSIS

The design of the data collection was a repeated measures design in which subjects were followed during a number of time intervals; in each interval the occurrence or nonoccurrence of an event was noted. The data base for the analysis consists of n subjects, each followed over a set of intervals. The number of intervals does not have to be constant for all subjects. For the present study, the subjects were the infants, the intervals were the two-week intervals, and the event was the occurrence of a respiratory illness.

The mathematical model selected for the occurrence of an event (respiratory illness) is a logit model in which the probability of an illness in a two-week period, P, is related to a set of independent variables, $X_1 \ldots X_k$, such as nitrogen dioxide exposure, age, gender, and birth order, by the formula:

$$\text{logit}(P) = \log(P/[1 - P]), = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p.$$

The parameters $\beta_0, \beta_1, \ldots \beta_p$, are to be estimated, for example, by iterative weighted least squares (Zeger and Liang 1992).

The main statistical inference procedure employed was the Generalized Estimating Equation (Zeger et al. 1988; Zeger and Liang 1992). This is a new procedure that has received widespread attention and is appropriate to the problem under investigation. The Generalized Estimating Equation mathematical model is similar to that of a multiple logistic regression model. However, in logistic regression, it is assumed that all individuals and intervals observed for an individual are independent. In the Generalized Estimating Equation procedure, the intervals observed for an individual are not assumed to be independent; the covariant structure of these intervals is modeled and taken into account in the estimating procedure. Although the estimation procedure is different than that used in ordinary logistic regression, the coefficients of the Generalized Estimating Equation have the same interpretation as those of a logistic regression. For example, if X_1 represents gender with X_1 = 1 or 0, depending on whether the infant is a male or female, then $\exp(\beta)_1$ can be viewed as the approximate ratio of the probability of an occurrence of a respiratory illness in males to that in females.

TECHNICAL EVALUATION

This was a carefully planned and well-executed study. It focused on infants, a population at increased risk, and adds substantially to the epidemiologic data base for examining the existence of an association between exposure to nitrogen dioxide and respiratory illness. Several aspects of the study design, exposure assessment, data analysis, and the investigators' results are discussed below. The following discussion is intended as a guide for understanding the results and for planning future investigations.

STUDY DESIGN

In any observational or experimental study of the effect of an exposure as variable as indoor air pollution on an out-

come as complex as respiratory illness, it is usually not possible to investigate or control all the possible confounding or effect-modifying factors. There are also practical constraints associated with the timing, location, and costs of the study. Thus, no single study design is likely to address all questions or provide results that can be generalized to all population groups.

The selection of a study population is an important element in study design, and one that has implications for generalizing the results. The strategy of recruiting four exposed infants (from homes with gas stoves) for every unexposed infant (from homes with electric stoves) was a sound approach for increasing the proportion of more highly exposed infants, and thus increasing the statistical power of the study to detect any effect if one were present. Excluding infants from homes with cigarette smokers was also an appropriate approach for reducing one of the most powerful confounding factors. In order to reduce potential confounding by nitrogen dioxide exposures outside the home, subjects were excluded if they spent more than 20 hours per week in day care. However, day-care attendance in itself is a risk factor for infectious diseases in children (The Child Day Care Infectious Disease Study Group 1984). For lower respiratory illness, Holberg and coworkers (1993) reported that the presence of three or more unrelated children in a day-care setting for at least nine hours a week was associated with an increased risk of lower respiratory illness for infants and children between the ages of four and 36 months. Excluding low-birth-weight and unhealthy infants reduced the number of determinants of respiratory illness under investigation, but limited the extent to which the results can be generalized.

The advantage of these restrictions in the study population is that the effect of nitrogen dioxide exposure could be evaluated in a relatively homogeneous sample of infants. The disadvantages are that the results cannot be generalized to the potentially more susceptible portions of the population, such as unhealthy babies (i.e., low-birth-weight babies and babies with premature lungs), infants with parents or care givers who smoke, and infants who attend day care. Recruitment of the study population was difficult, and the protocol was demanding. Only 823 of the 1,315 study subjects were followed until 18 months of age; 1,205 infants completed at least one month of observation and are the subjects used in this analysis. Those with less than 30 days of observation were excluded from the analysis.

EXPOSURE ASSESSMENT

Compared with most epidemiologic studies of air pollution, particular care was taken with the exposure assessment portion of this study. In addition to obtaining repeated measurements of nitrogen dioxide concentrations in multiple locations in the subjects' homes throughout the entire observation period, the investigators designed and followed well-defined quality control and quality assurance procedures, paying careful attention to a variety of factors that might potentially affect the collection of the nitrogen dioxide data. Rigorous procedures to follow up and track sample collections were implemented, resulting in the most thorough evaluation of indoor and outdoor exposures that has been conducted in epidemiologic studies of the health effects of exposure to nitrogen dioxide.

The investigators obtained integrated two-week measurements of nitrogen dioxide concentrations. For subjects in homes with gas stoves, they obtained measurements every two weeks in the infants' bedrooms. During the colder seasons, they obtained additional measurements every other month in the kitchen and activity room. For subjects living in homes with electric stoves, they obtained the measurements in the infants' bedrooms during alternate two-week periods. Thus, there were some gaps in the time-series data because of the sampling design; others occurred because of problems in the parents' use of the Palmes tubes and the laboratory analysis. Additionally, some measurements were excluded from the analysis because they did not meet the criteria for limits of detection or seasonal variability. The median number of days with missing data was 33 (8% of the total observation days) for children living in homes with gas stoves and 188 (48% of the total observation days) for those in homes with electric stoves. These gaps were covered by straight line interpolation from the bounding measurements. The majority of the interpolated nitrogen dioxide levels were performed for homes with electric stoves, where the temporal variability in nitrogen dioxide levels is low. The interpolation technique, which was discussed in detail in a communication to the Health Review Committee, appears appropriate, but it may have diminished the variability in the nitrogen dioxide levels, thereby reducing significance.

ILLNESS SURVEILLANCE

Careful documentation of the occurrence and types of respiratory illnesses is another feature of this study that sets it apart from many earlier epidemiologic investigations of the health consequences of nitrogen dioxide exposure. In addition to the parental diaries for recording respiratory symptoms, the protocol included examination by a nurse practitioner during illness events and the procurement of nasal specimens for viral culture in selected subjects. The clinical evaluation provided a standard data base against

which the primary surveillance data could be compared. Information on the comparability of parental reports of respiratory illness with the clinical diagnoses was presented in a draft manuscript that was available to the Technical Review Panel (Samet et al. 1993). These data, which will be published in Part III of Research Report Number 58, indicate that the surveillance system used in this study was sufficiently sensitive to determine the presence of both upper and lower respiratory illnesses. However, whereas 93.4% of the subjects' illnesses classified as lower respiratory infections by the surveillance system were similarly classified by the nurse practitioner, the figure was only 21.6% for upper respiratory illnesses. The majority of false positive reports of lower respiratory illness were for children who had wet cough only. In addition, virologic studies of nasal washings from symptomatic children showed a rather low yield. A virus was isolated from 21% of 670 cultures; the isolation rate was 23.8% for children classified as having a lower respiratory illness. These isolation rates are substantially lower than those of Wright and coworkers (1989), who reported a greater than 60% viral isolation rate for children diagnosed as having a lower respiratory illness by a pediatrician. Because appropriate techniques were used for the virologic studies, it is likely that some of the respiratory diseases did not have a viral etiology, at least for those agents that were examined. Thus, the health outcomes were appropriately designated as respiratory illnesses rather than respiratory infections.

These clinical findings demonstrate how difficult it is to ascertain the presence of lower respiratory infections in a community study and to determine the etiologic agents involved. The authors defined any subject with at least two consecutive days of runny or stuffy nose, and trouble breathing with wet cough or wheezing, as having a lower respiratory illness. However, as the investigators readily show, not all these subjects had infections that could be easily diagnosed as such.

DATA ANALYSIS

The new Generalized Estimating Equation used for the final analysis was appropriate for this study. Although there are some concerns with its implementation because of the effect on the analysis of the assumed covariant structure among the time intervals, it is reassuring that in the present study, the investigators explored different covariant structures and found that the results did not change. Another concern is the computer time it takes to perform this type of analysis, which limits the number of multivariate analyses that can be performed.

STATISTICAL POWER

A major concern with the study is whether it had adequate statistical power to detect health effects caused by exposure to elevated concentrations of nitrogen dioxide. Because only 5% of the exposures were above 40 ppb, the investigators devised a clever procedure for estimating statistical power. For dealing with the incidence of respiratory illness, the investigators assumed that the sampling distribution of the coefficient quantifying the effect of nitrogen dioxide was normally distributed, and that the standard error of this distribution was equal to that observed in the study data. With these two assumptions, it was possible to estimate how large the odds ratio would need to be to attain 80% and 90% power. The estimation consisted of finding the value of the coefficient (taken as the mean of a normal distribution with standard error equal to the observed values) that has an 80% probability of rejecting the null hypothesis with an odds ratio of unity. If β is the coefficient, then $\exp(\beta)$ is the odds ratio. Table 11 in Part I of the Investigators' Report contains the values of these odds ratios that correspond to 80% and 90% power.

Two concerns are raised by the procedure and its results. First, some of the assumptions of the procedure may not be correct, especially the assumption of the constant standard error of the coefficients. The standard error of the model coefficient may be a function of the magnitude of the coefficient, so that the larger the coefficient, the larger the standard error. The effect of this could be to reduce the magnitude of the power, or, equivalently, to increase the size of the odds ratio needed to attain 80% or 90% power. Unfortunately, because the study did not produce any statistically significant results, it is not possible to estimate whether the standard errors of the coefficients increased with the magnitude of the coefficients. Second, assuming the method of power calculations to be correct, there is limited power for an important category, the incidence of lower respiratory illness with wheezing. This can be seen in Table 11 of Part I, in which the odds ratio would have to be as high as 1.89 (comparing nitrogen dioxide levels greater than 40 ppb with nitrogen dioxide less than 20 ppb) in order to attain 80% power for the category of lower respiratory illness with wheezing.

RESULTS AND INTERPRETATION

The primary end points of this study are the health outcomes (incidence and duration of respiratory illness) in infants and toddlers under 18 months of age for the following nitrogen dioxide exposure categories: low (0 to 20 ppb), medium (20 to 40 ppb), and high (greater than 40 ppb).

These results are presented in Part I of the report. Part II presents the results of the assessment of indoor nitrogen dioxide levels, which form the basis of the analysis in Part I, time-activity data for the subjects, and the results of microenvironmental modeling to estimate personal exposures to nitrogen dioxide.

Exposure Assessment

A comprehensive set of indoor and outdoor nitrogen dioxide concentrations was obtained using state-of-the-art methods. More than 36,000 indoor nitrogen dioxide measurements were made in the kitchens, activity rooms, and bedrooms of 1,205 subjects; in addition, more than 1,000 outdoor measurements were made at 11 monitoring sites around the city. The distributions of the two-week average nitrogen dioxide measurements (Part II, Figure 2) indicate that for this study population, the mean indoor nitrogen dioxide concentrations during the winter (October through March) in homes with gas cooking stoves were 21, 29, and 34 ppb for the bedroom, living room, and kitchen, respectively, with few observations above 40 ppb. During the summer (April through September), bedroom nitrogen dioxide concentrations in homes with gas stoves averaged 14 ppb; for homes with electric cooking stoves, the mean bedroom concentration was 7 ppb for both seasons.

The mean indoor concentrations observed in the present study, particularly for the bedroom (which accounted for a large portion of the total exposure), fall between the low end and middle range, rather than toward the high end, of average indoor concentrations reported in some studies of homes with gas stoves or other sources of indoor nitrogen dioxide (Table 2). For example, two large-scale studies in Southern California, where outdoor nitrogen dioxide can make a major contribution to indoor levels, found one-week average nitrogen dioxide concentrations of 40 and 54 ppb for the kitchen and 30 and 36 ppb for the bedroom in homes with gas stoves (Wilson et al. 1986). (Even higher nitrogen dioxide concentrations were reported in homes that had gas floor furnaces.) In a study of New York City apartments with gas appliances, Goldstein and coworkers (1985), using a two-day averaging time, observed average nitrogen dioxide concentrations in the kitchen and bedroom in the ranges of 50 to 66 ppb and 35 to 50 ppb, respectively. These inner-city apartments were small and poorly ventilated, and, in contrast to the California situation, indoor sources were primarily responsible for the elevated nitrogen dioxide levels. It is important to note that Drs. Samet and Spengler made repeated nitrogen dioxide measurements throughout the year and then expressed their nitrogen dioxide concentrations as six-month averages. This reduced the contribution of any random high excursions from the reported means.

It is unfortunate that despite careful pilot studies to develop methods for monitoring exposure and outcome and for validating these measures, levels of nitrogen dioxide were actually lower in this study than in the two pilot studies (Samet and Spengler 1989). For example, mean values in infants' bedrooms were 33 and 31 ppb (two different sampling cycles) for homes with gas stoves in the first pilot study, and 30 and 23 ppb in the second pilot study. Pilot Study II was conducted between January and March 1986, whereas Pilot Study I data were collected two years earlier, during November and December. Climatic factors, such as warmer temperatures, less frequent inversions, and increased ventilation of homes, were cited as reasons for the lower nitrogen dioxide levels in Pilot Study II. The investigators speculate that changes in cooking habits over the last decade, especially the increased use of microwave ovens, may have been responsible for the fact that lower levels of nitrogen dioxide were found in homes in Albuquerque in this study (conducted from 1988 to 1991) than in the pilot studies.

Time-activity data for the subjects also yielded important information. The investigators reported that infants spent 50% of their time in their bedrooms, providing justification for using bedroom nitrogen dioxide levels as the exposure variable in this population. They also determined that for homes with gas stoves, bedroom nitrogen dioxide levels compared favorably to the time-weighted averages calculated using a microenvironmental model. The mean difference between microenvironmental exposure estimates and the bedroom nitrogen dioxide concentrations was 1.4 ppb.

Health Outcomes

In this study population, there was no uniform trend of increasing illness incidence rates with increasing exposure to nitrogen dioxide (Part I, Table 3 and Appendix A). When the Generalized Estimating Equation was used to examine the effect of nitrogen dioxide exposure on illness occurrence during two-week observation intervals, none of the odds ratios were significantly elevated for unlagged nitrogen dioxide exposures (the two-week average for the corresponding two-week observation interval), for lagged nitrogen dioxide exposure (the two-week average for the preceding two-week observation interval), or for stove type (gas or electric). Similar results were obtained when illness incidence rates were examined within strata defined by nitrogen dioxide exposure levels and potential confounding or modifying variables (atopy, asthma, breast feeding, income, and maternal education) (Part I, Table 4). The investigators reported a nonsignificant increase in the odds ratio (odds ratio = 1.95; 95% CI 0.90, 4.22) for the effect of nitrogen dioxide exposure on the incidence of lower respi-

ratory illness with wheezing in 36 subjects diagnosed as having asthma (Part I, Table 8). One positive finding was the effect of short periods of time in day care on the increased incidence of respiratory illness in children up to 18 months of age.

Although the data on the incidence of the different categories of upper and lower respiratory illness are consistent in showing no association with the presence of gas stoves or nitrogen dioxide exposure, the findings on illness duration are not as uniform. When the median duration of illness was examined, there was no significant association between nitrogen dioxide exposure and the duration of upper respiratory illness, lower respiratory illness, or lower respiratory illness with wet cough. However, there was a nonsignificant increase in the duration of illnesses classified as lower respiratory illness with wheezing with increasing nitrogen dioxide levels (Part I, Table 9). Multivariate modeling adjusting for the effect of 11 other variables showed no effect of nitrogen dioxide exposure or illness duration for the illness categories of upper respiratory illness and all lower respiratory illness. In this analysis, there was a small but significant decrease in the duration of lower respiratory illness with wet cough in the highest exposure category. There was also a nonsignificant increase in the duration of illnesses for the category of lower respiratory illness with wheezing as nitrogen dioxide exposure increased (Part I, Table 10). Figure 5 in Part I suggests some differences in illness duration between the low-exposure and the high-exposure groups.

Few epidemiologic studies have employed methods sufficiently sensitive to track respiratory symptoms over time in order to distinguish between illness incidence and duration. In the one other study that examined both outcomes (Braun-Fahrländer et al. 1992), a six-week study of 625 Swiss preschool children (40% of whom were under two years of age), nitrogen dioxide had no association with the incidence of respiratory symptoms. However, there was a small increase in the duration of respiratory episodes (relative duration = 1.13; 95% CI = 1.01, 1.27) with increasing outdoor (but not indoor) nitrogen dioxide levels. An effect of nitrogen dioxide exposures on illness duration, which is an indicator of the severity of an infectious episode, agrees with the findings of the animal infectivity model. Those findings suggest that nitrogen dioxide may affect an animal's ability to control an infection.

A key consideration in interpreting the generally negative results reported in the Samet study is whether or not the study had sufficient statistical power to detect effects due to high exposures. Figure 1 in Part I of the Investigators' Report indicates that the percentage of observation days in the high-exposure group was small. Only 5% of the observation time was classified as high nitrogen dioxide exposure (greater than 40 ppb), and only 23% of the exposures were greater than 20 ppb. Although the investigators are correct in stating that the Albuquerque exposures are representative of many other communities in the United States, this does not address the important question of whether there are elevated risks for nitrogen dioxide exposures at levels higher than 40 ppb. Such high exposures can occur in residences with unvented kerosene or gas heaters, in urban locations in the Northeast where gas stoves may be used for heating, or in heavily polluted areas such as Los Angeles, where the annual mean nitrogen dioxide concentration outdoors is greater than 40 ppb. For the high nitrogen dioxide exposure range (greater than 40 ppb), this study had poor statistical power to detect an effect of nitrogen dioxide exposure on illnesses categorized as lower respiratory illness with wheezing. Because, as was discussed earlier, it is not possible to determine whether some of the underlying assumptions of the statistical power estimate are correct, the question of power for the other end points is unresolved.

Comparison with Other Studies

There is remarkable internal consistency among the findings of this study in that no significant association was found between infants' exposure to nitrogen dioxide and either the incidence or the duration of respiratory illness. The one exception was the duration of lower respiratory illnesses with wheezing, for which a nonsignificant increase (odds ratio = 1.41; CI = 0.95, 2.09) was observed in the high-exposure (greater than 40 ppb) group. Although these generally negative results agree with the findings of some infant studies (Melia et al. 1983; Margolis 1992), they appear to be at variance with other studies in which a significant increase in at least one parameter related to respiratory health was reported for subjects living in homes with gas stoves (Speizer 1980; Ekwo et al. 1983; Ware et al. 1984; Dockery et al. 1989). However, examining the point estimates and confidence intervals for the infant studies (Figure 2) indicates that, with the exception of the Ekwo study, findings of this study and those of the other infant studies generally agree well. In studies in which positive effects were observed, they have generally been small and only marginally significant, suggesting that any effect of indoor nitrogen dioxide exposure on respiratory illness in infants is likely to be small and easily obscured if the subjects are misclassified with regard either to exposure or respiratory symptoms. Such misclassification can have a profound effect on the outcome of a study; the direction of the effect depends on whether the misclassification is differential or nondifferential. Nondifferential misclassification usually biases toward the null value (indicating no effect or un-

derestimating an effect), whereas differential misclassification can lead to biases in either direction.

The ability of any study to ascertain small changes in illness rates in response to low pollutant concentrations depends, in part, on the reliability and sensitivity of the measurement instrument. The nitrogen dioxide exposure assessment in this study represents a major improvement over many earlier investigations that relied on surrogate information, such as the presence of a gas stove or heater. By measuring nitrogen dioxide exposures over the entire observation period (18 months), the investigators provided more reliable measures of the actual nitrogen dioxide exposures of the study population than by estimating long-term exposures from single one-week or two-week measurements. If misclassification of exposure had been obscuring a real effect of nitrogen dioxide, obtaining improved exposure estimates should have increased the likelihood of observing a relationship between nitrogen dioxide exposure and respiratory illness.

The second potential source of bias, misclassification of the outcome measure, was addressed in this study by using daily symptom diaries rather than parental questionnaires to determine episodes of respiratory illness during the previous year or during infancy. The validation procedures that were used to confirm the parental reports of respiratory illness and the protocol for classifying symptoms provide more sensitive and accurate indicators of respiratory symptoms than retrospective questionnaires. Again, although these procedures should have reduced misclassification and thus increased the likelihood of observing an effect, the investigators found no significant effect of nitrogen dioxide exposure in this population.

Other differences in the design of studies that have examined the influence of nitrogen dioxide exposure on respiratory illnesses in infants and older children include differences in the study populations and the role of confounding variables. Indoor nitrogen dioxide studies have been conducted in disparate geographic locations (Northern Europe, United Kingdom, and various regions of the United States); these locales differ markedly in their climate, populations, and type of housing. It is possible that confounding variables may be producing spurious associations in some studies. For example, indoor studies in northern latitudes have found an association between humidity or home dampness and respiratory illness in children (Florey et al. 1979; Dijkstra et al. 1990). Florey and coworkers (1979) suggested that a combination of high humidity and low temperature, rather than elevated nitrogen dioxide, might contribute to the observed association between indoor nitrogen dioxide exposure and the prevalence of respiratory symptoms in British schoolchildren. When they tested this hypothesis in a small sample of children (five to six years of age), they found a weak association between high humidity and the prevalence of having one or more respiratory symptoms (Melia et al. 1982). Dijkstra and coworkers (1990) found that respiratory symptoms in Dutch children were associated with exposure to tobacco smoke and home dampness, but not with indoor levels of nitrogen dioxide. A recent report that the previous day's levels of outdoor total suspended particles was a significant predictor of the incidence of upper respiratory symptoms in Swiss preschool-children supports the hypothesis that, in some studies, nitrogen dioxide measurements may be a surrogate for other pollutant exposures (Braun-Fahrländer et al. 1992). However, in the U.S. studies, particles do not appear to be important confounders. In the Six Cities studies, the level of respirable particles was 6 $\mu g/m^3$ higher in homes with a source of nitrogen dioxide than in homes with no gas stove or heater, and this factor was treated as a covariate in the analysis (Neas et al. 1991). In their pilot studies, Drs. Samet and Spengler (1989) reported that homes in Albuquerque with high and low levels of nitrogen dioxide did not differ in their levels of respirable-sized particles.

Although exposure to nitrogen dioxide levels in excess of those encountered in this study may be causally related to the incidence or severity of respiratory illness in children, other data indicate that an effect, if it exists, is subtle and may be difficult to distinguish from other environmental risk factors, especially environmental tobacco smoke. The positive effects that have been reported for nitrogen dioxide on respiratory illness in children have odds ratios that range from 0.94 to 1.53 (as estimated by Hasselblad et al. 1992) and are smaller than those reported for passive smoking. For example, Wright and coworkers (1991) reported that the odds of having a lower respiratory illness were 1.5 to 2.8 times higher in infants whose mothers smoked than those whose mothers were nonsmokers. Maternal smoking was also related to an early age of first respiratory illness. A recent EPA report on the effects of passive smoking on respiratory disorders reviewed all studies of environmental tobacco smoke and respiratory disease and estimated that the risk of having an acute respiratory illness was 1.5 to 2.0 times higher for young children who were exposed to parental tobacco smoke than for those living in households where there were no smokers (U.S. Environmental Protection Agency 1992b). In those studies that have reported a positive association between nitrogen dioxide and respiratory illness in children, the odds ratios have generally been under 1.5 (Appendix A) (Hasselblad et al. 1992).

The passive smoking data and the epidemiologic data on the age distribution of respiratory illnesses suggest that infants and toddlers are at higher risk for developing respiratory illnesses as a result of an environmental insult than older children or adults. For example, the increased risk as-

sociated with environmental tobacco smoke is highest in infants and toddlers under the age of 18 months; the increased risk continues until approximately three years of age and then declines (U.S. Environmental Protection Agency 1992b). These findings are in contrast with the nitrogen dioxide literature that documents the strongest associations for children over six years of age. If passive smoke and nitrogen dioxide increase susceptibility to infections through the same mechanisms, then studies in infants should have a higher likelihood of detecting an effect than studies in schoolchildren. Although smoking was not controlled in some early studies (Melia 1977; Keller et al. 1979a,b), it has been controlled in recent investigations by employing a sampling strategy that includes equal numbers of smokers and nonsmokers (Neas et al. 1991) or by adjusting for smoking in the analysis (Florey 1979; Melia 1979; Ekwo et al. 1983; Ware et al. 1984; Ogston et al. 1985; Dijkstra 1990). However, smoking remains a potential confounder in any evaluation of low-level exposures to other indoor air pollutants.

Public Health Implications

The importance of the findings of this study lie in the fact that no significant association between nitrogen dioxide exposure (in the range of 0 to 40 ppb) and respiratory illness was found in healthy infants and toddlers when every precaution was taken to eliminate potentially confounding variables, to adjust for the variables that could not be eliminated, to validate the outcome measures, and to obtain accurate exposure information.

In interpreting the public health implications of these findings, the study's strengths and limitations need to be considered. The strengths include:

1. Subjects were infants and toddlers at the age of highest risk for respiratory infections;
2. Subjects were monitored prospectively from birth to 18 months of age;
3. The exposure measurements were conducted carefully, and nitrogen dioxide levels were monitored in the homes of the subjects throughout the observation period (18 months);
4. Appropriate measures were used to validate the health outcomes; and
5. The influence of important confounding factors, exposure to passive smoke and day care, was controlled.

The limitations of the study relate to:

1. The relatively small number of homes in which the nitrogen dioxide exposures were greater than 40 ppb (77% of the observations were less than 20 ppb; 18% were between 20 and 40 ppb; only 5% were greater than 40 ppb); and
2. The limited ability to generalize the results to more susceptible populations (premature babies, babies with low birth weight, babies with respiratory problems, infants who spend a large proportion of their time in day care, and those exposed to tobacco smoke).

IMPLICATIONS FOR FUTURE RESEARCH

This study produced an extensive data set, and although the investigators have done an admirable job of analyzing it, many fruitful analyses remain to be performed. Some of these might involve the analysis of subsets of the data. These analyses will be post hoc and will need confirmation from other studies; however, they appear to be worth performing. For example, it may be worthwhile to pursue a subset for which there are relations of variables with illness duration or with lower respiratory illness with wheezing.

Another useful line of future research would be to perform the multivariate Generalized Estimating Equation analyses without so many covariates being considered simultaneously. In the present analyses, at least 11 variables were entered into the multivariate analyses. These include season, age, gender, ethnicity, birth order, day-care status, income, maternal education, breast feeding, parental atopy and asthma, and a maternal symptom report. These analyses are unable to sort out the effects of the various variables. Because of the extensive computer time required for the Generalized Estimating Equation analysis, the investigators had little choice but to conduct a simultaneous analysis. A rethinking of these analyses with an investigation of the separate and combined variables may be informative. Lastly, an investigation of the effect of missing data may prove important.

The present study does not address the upper tails of the distributions of outdoor and indoor nitrogen dioxide concentrations observed in some urban regions of the United States and under certain gas and kerosene appliance use scenarios not encountered in this study. Whether it is cost effective to conduct additional future studies that might have greater applicability to populations exposed to nitrogen dioxide levels in excess of 40 ppb should be explored.

Finally, future research might include studies with a broader spectrum of infants, especially a subset of infants who may be at higher risk.

SUMMARY AND CONCLUSIONS

Drs. Jonathan Samet, John Spengler, and colleagues conducted this study to evaluate whether indoor exposure to nitrogen dioxide increases the incidence or the duration, or

both, of respiratory illness in infants. This issue is important because acute respiratory illnesses in the first two years of life, while quite common, can lead to hospitalization and might be associated with manifestations of chronic lung disease in later life. Earlier epidemiologic studies that examined this relationship have produced conflicting results, possibly because of misclassification of exposure or health outcomes.

The study was a prospective cohort study involving a restricted population of 1,205 infants in Albuquerque, NM. Subjects were healthy infants and toddlers; babies with low birth weight, congenital abnormalities, or underlying respiratory disease were excluded from the study. The investigators made every attempt to avoid misclassification of exposure and the health outcomes by monitoring nitrogen dioxide levels in subjects' homes during the entire observation period and by collecting information about respiratory illnesses prospectively, using appropriate validation procedures. Confounding by two major determinants of respiratory infection in children was reduced by selecting infants whose parents did not intend to use day care and who lived in homes where there were no smokers; subjects were dropped from the study if they spent more than 20 hours a week in day care. Other potential confounding factors were controlled in the analysis.

The investigators found no association between nitrogen dioxide exposure and the incidence rates of either upper or lower respiratory illness. When the Generalized Estimating Equation approach was used to examine the effect of nitrogen dioxide exposure on illness occurrence during two-week observation intervals, none of the odds ratios was significantly elevated for unlagged nitrogen dioxide exposure, lagged nitrogen dioxide exposure, or stove type. Similar results were obtained when illness rates were examined within strata defined by nitrogen dioxide exposure and potential confounding or modifying variables (atopy, asthma, breast feeding, income, and maternal education).

When duration of illness was examined, there was no significant association of nitrogen dioxide and the duration of upper respiratory illness, lower respiratory illness, and lower respiratory illness with wet cough. Further multivariate modeling using 11 indicator variables showed no significant increase of the illness categories with increasing nitrogen dioxide exposure. However, there was a nonsignificant increase in the duration of illnesses classified as lower respiratory illness with wheezing in the highest nitrogen dioxide exposure category (greater than 40 ppb).

A key consideration in interpreting these results is the level of nitrogen dioxide to which the children were exposed. During the winter, the mean nitrogen dioxide concentrations in homes with gas cooking stoves were 21, 29, and 34 ppb for the bedroom, living room, and kitchen, respectively; few bedroom observations exceeded 40 ppb. During the summer, bedroom nitrogen dioxide concentrations in homes with gas stoves averaged 14 ppb, whereas in homes with electric cooking stoves, the mean bedroom concentration was 7 ppb for both seasons. Approximately 77% of the bedroom nitrogen dioxide observations were less than 20 ppb; only 5% were greater than 40 ppb. Although these values are consistent with some reports of indoor levels of nitrogen dioxide, the mean concentrations, particularly for the bedroom (which accounted for a large portion of the infants' exposure), fall between the low end and middle range, rather than the high end of indoor nitrogen dioxide concentrations reported in some studies of homes with gas appliances. There are also polluted urban environments where the outside average nitrogen dioxide concentrations exceed 40 ppb. Therefore, the investigators' results may not apply to infants who are exposed to average nitrogen dioxide concentrations substantially in excess of 40 ppb.

This study is one of the most carefully designed and executed studies of the effects of nitrogen dioxide on respiratory illness that has been conducted to date. The findings are important because they indicate that in a population of healthy infants and toddlers, no significant associations between nitrogen dioxide exposure (in the range of 0 to 40 ppb) and respiratory illness were found when every precaution was taken to make an accurate assessment of exposure, to validate the measurements of respiratory illness, to eliminate potentially confounding variables, and to adjust for the variables that could not be eliminated.

ACKNOWLEDGMENTS

The Health Review Committee wishes to thank the members of the outside Technical Review Panel for their help in evaluating the scientific merit of the Investigators' Report and their contributions to the Committee's Commentary. The Committee also acknowledges Dr. Kathleen M. Nauss for her assistance in preparing the Commentary, Ms. Virgi Hepner for overseeing the publication of this report, and Ms. Andrea Cohen and Ms. Mary-Ellen Patten for their editorial and administrative support.

REFERENCES

Acton JD, Myrvik QN. 1972. Nitrogen dioxide effects on alveolar macrophages. Arch Environ Health 24:48–52.

Azoulay-Dupuis E, Torres M, Soler P, Moreau J. 1983. Pul-

monary NO_2 toxicity in neonate and adult guinea pigs and rats. Environ Res 30:322–339.

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

Barker DJP, Osmond C. 1986. Childhood respiratory infection and adult chronic bronchitis in England and Wales. Br Med J 293:1271–1275.

Bauer MA, Utell MJ, Morrow PE, Speers DM, Gibb FR. 1986. Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. Am Rev Respir Dis 134:1203–1208.

Braun-Fahrländer C, Ackermann-Liebrich U, Schwartz J, Gnehm HP, Rutishauser M, Wanner HU. 1992. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis 145:42–47.

Braun-Fahrländer C, Ackermann-Liebrich U, Wanner H-U, Rutishauser M, Gnehm HE, Minder CE. 1989. Auswirkungen von luftschadstoffen auf die atemwege von kleinkindern. Schwiez med Wochenschr 119:1424–1433.

Busse WW. 1989. The relationship between viral infections and onset of allergic diseases and asthma. Clin Exp Allergy 19:1–9.

Butler DA, Ozkaynak H, Billick IH, Spengler JD. 1990. Predicting indoor NO_2 concentrations as a function of home characteristics and ambient NO_2 levels. In: Indoor Air '90: Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Vol. 2, Characteristics of Indoor Air, July-August, Toronto, Ontario, Canada, pp. 519–524. International Conference on Indoor Air Quality and Climate, Ottawa, Ontario, Canada.

Bylin G, Lindvall T, Rehn T, Sundin B. 1985. Effects of short-term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function. Eur J Respir Dis 66:205–217.

California Environmental Protection Agency Air Resources Board. 1992a. Review of the one-hour ambient air quality standard for nitrogen dioxide: Staff report. California Air Resources Board Research Division, Sacramento, CA.

California Environmental Protection Agency Air Resources Board. 1992b. Review of the one-hour ambient air quality standard for nitrogen dioxide: Technical support document. California Air Resources Board Research Division, Sacramento, CA.

The Child Day Care Infectious Disease Study Group. 1984. Public health considerations of infectious diseases in child day care centers. J Pediatr 105:683–701.

Davis JK, Davidson M, Schoeb TR. 1991. Murine Respiratory Mycoplasmosis: A Model to Study Effects of Oxidants. Research Report Number 47. Health Effects Institute, Cambridge, MA.

Davis JK, Davidson M, Schoeb TR, Lindsey JR. 1992. Decreased intrapulmonary killing of *Mycoplasma pulmonis* after short-term exposure to NO_2 is associated with damaged alveolar macrophages. Am Rev Respir Dis 145:406–411.

Denny FW, Clyde WA Jr. 1986. Acute lower respiratory tract infections in nonhospitalized children. J Pediatr 108:635–646.

Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JSM. 1990. Respiratory health effects of the indoor environment in a population of Dutch children. Am Rev Respir Dis 142:1172–1178.

Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG Jr. 1989. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 139:587–594.

Ekwo EE, Weinberger MM, Lachenbruch PA, Huntley WH. 1983. Relationship of parental smoking and gas cooking to respiratory disease in children. Chest 84:662–668.

Ferris BG. 1978. Health effects of exposure to low levels of regulated air pollutants: A critical review. J Air Pollut Control Assoc 28:482–497.

Florey C du V, Melia RJ, Chinn S, Goldstein BD, Brooks AGF, John HH, Craighead IB, Webster X. 1979. The relation between respiratory illness in primary schoolchildren and the use of gas for cooking: III. Nitrogen dioxide, respiratory illness and lung infection. Int J Epidemiol 8:347–353.

Gardner DE, Miller FJ, Bloomer EJ, Coffin DL. 1979. Influence of exposure mode on the toxicity of NO_2. Environ Health Perspect 30:23–29.

Glezen WP. 1989. Antecedents of chronic and recurrent lung disease. Am Rev Respir Dis 140:873–874.

Goings SAJ, Kulle TJ, Bascom R, Sauder LR, Green DJ, Hebel JR, Clements ML. 1989. Effect of nitrogen dioxide exposure on susceptibility to influenza A virus infection in healthy adults. Am Rev Respir Dis 139:1075–1081.

Gold DR, Tager IB, Weiss ST, Tosteson TD, Speizer FE. 1989. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. Am Rev Respir Dis 140:877–884.

Goldstein BD, Melia RJW, Chinn S, Florey C du V, Clark D, John HH. 1979. The relation between respiratory illness in primary schoolchildren and the use of gas for cooking: II. Factors affecting nitrogen dioxide levels in the home. Int J Epidemiol 8:339–345.

Goldstein E, Eagle C, Hoeprich PD. 1973. Effect of nitrogen dioxide on pulmonary bacterial defense mechanisms. Arch Environ Health 26:202–204. Air Pollution Control Association, Pittsburgh, PA.

Goldstein IF, Hartel D, Andrews LR. 1985. Monitoring personal exposure to nitrogen dioxide. In: Proceedings of the 78th Annual Meeting of the Air Pollution Control Association. Paper Number 85–85.7.

Goren AI, Hellmann S. 1988. Prevalence of respiratory symptoms and diseases in schoolchildren living in a polluted and in a low polluted area in Israel. Environ Res 45:28–37.

Graham JA, Gardner DE, Blommer EJ, House DE, Ménache MG, Miller FJ. 1987. Influence of exposure patterns of nitrogen dioxide and modifications by ozone on susceptibility to bacterial infectious disease in mice. J Toxicol Environ Health 21:113–125.

Graham NMH. 1990. The epidemiology of acute respiratory infections in children and adults: A global perspective. Epidemiol Rev 12:149–178.

Hammer DI, Hasselblad V, Portnoy B, Wehrle PF. 1974. Los Angeles student nurse study: Daily symptom reporting and photochemical oxidants. Arch Environ Health 28:255–260.

Hasselblad V, Eddy DM, Kotchmar DJ. 1992. Synthesis of environmental evidence: Nitrogen dioxide epidemiology studies. J Air Waste Manage Assoc 42:662–671.

Hazucha MJ, Ginsberg JF, McDonnell WF, Haak ED Jr, Pimmel RL, House DE, Bromberg PA. 1982. Changes in bronchial reactivity of asthmatics and normals following exposures to 0.1 ppm NO_2. In: Air Pollution by Nitrogen Oxides: Proceedings of the U.S.-Dutch International Symposium (Schneider T, Grant L, eds.) pp. 387–400. Elsevier Science Publishing Co., New York, NY.

Hedberg K, Hedberg CW, Iber C, White KE, Osterholm MT, Jones DBW, Flink JR, MacDonald KL. 1989. An outbreak of nitrogen dioxide–induced respiratory illness among ice hockey players. JAMA 262:3014–3017.

Holberg CJ, Wright AL, Martinez FD, Morgan WJ, Taussig LM, Group Health Medical Associates. 1993. Child day care, smoking by caregivers, and lower respiratory tract illnesses in the first 3 years of life. Pediatrics 91:1–8.

Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM. Lebowitz MD, Group Health Medical Associates. 1991. Risk factors for respiratory syncytial virus–associated lower respiratory illnesses in the first year of life. Am J Epidemiol 133:1135–1151.

Jacobsen J, Smith TA, Hurley JF, Robertson A, Roscrow R. 1988. Respiratory Infections in Coal Miners Exposed to Nitrogen Oxides. Research Report Number 18. Health Effects Institute, Cambridge, MA.

Jakab GJ. 1988. Modulation of Pulmonary Defense Mechanisms Against Viral and Bacterial Infections by Acute Exposures to Nitrogen Dioxide. Research Report No. 20. Health Effects Institute, Cambridge, MA.

Kagamimori S, Katoh T, Naruse Y, Watanabe M, Kasuya M, Shinkai J, Kawano S. 1986. The changing prevalence of respiratory symptoms in atopic children in response to air pollution. Clin Allergy 16:299–308.

Keller MD, Lanese RR, Mitchell RI, Cote RW. 1979a. Respiratory illness in households using gas and electricity for cooking: I. Survey of incidence. Environ Res 19:495–503.

Keller MD, Lanese RR, Mitchell RI, Cote RW. 1979b. Respiratory illness in households using gas and electricity for cooking: II. Symptoms and objective findings. Environ Res 19:504–515.

Koenig JQ, Covert DS, Morgan MS, Horike M, Horike N, Marshall SG, Pierson WE. 1985. Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. Am Rev Respir Dis 132:648–651.

Koenig JW, Pierson WE, Marshall SG, Covert DS, Morgan MS, VanBelle G. 1987. The Effects of Ozone and Nitrogen Dioxide on Lung Function in Healthy and Asthmatic Adolescents. Research Report Number 14. Health Effects Institute, Cambridge, MA.

Kubota K, Murakami M, Takenaka S, Kawai K, Kyono H. 1987. Effects of long-term nitrogen dioxide exposure on rat lung: Morphological observations. Environ Health Perspect 73:157–169.

Kulle TJ, Clements ML. 1988. Susceptibility to Virus Infection with Exposure to Nitrogen Dioxide. Research Report Number 15. Health Effects Institute, Cambridge, MA.

Leaderer BP, Zagraniski RT, Berwick M, Stolwijk JAJ. 1986.

Assessment of exposure to indoor air contaminants from combustion sources: Methodology and application. Am J Epidemiol 124:275–289.

Lebowitz MD, Holberg CJ, Boyer B, Hayes C. 1985. Respiratory symptoms and peak flow associated with indoor and outdoor air pollutants in the Southwest. J Air Pollut Control Assoc 35:1154–1158.

Linn WS, Shamoo DA, Spier CE, Valencia LM, Anzar UT, Venet TG, Avol EL, Hackney JD. 1985. Controlled exposure of volunteers with chronic obstructive pulmonary disease to nitrogen dioxide. Arch Environ Health 40:313–317.

Lowry T, Schuman LM. 1956. "Silo-filler's disease": A syndrome caused by nitrogen dioxide. JAMA 162:153–160.

Margolis PA, Greenberg RA, Keyes LL, LaVange LM, Chapman RS, Denny FW, Bauman KE, Boat BW. 1992. Lower respiratory illness in infants and low socioeconomic status. Am J Public Health 82:1119–1126.

Mauderly JL, Bice DE, Carpenter RL, Gillett NA, Henderson RF, Pickrell JA, Wolff RK. 1987. Effects of Inhaled Nitrogen Dioxide and Diesel Exhaust on Developing Lung. Research Report Number 8. Health Effects Institute, Cambridge, MA.

Melia J, Florey C du V, Sittampalam Y, Watkins C. 1983. The relation between respiratory illness in infants and gas cooking in the U.K.: A preliminary report. In: Proceedings of the 6th World Congress in Air Quality, August 16–20, 1983, pp. 263–269. International Union of Air Pollution Prevention Associations, Paris, France.

Melia RJW, Florey C du V, Altman DG, Swan AV. 1977. Association between gas cooking and respiratory disease in children. Br Med J (Clin Res Ed) 2:149–152.

Melia RJW, Florey C du V, Chinn S. 1979. The relation between respiratory illness in primary schoolchildren and the use of gas for cooking: I. Results from a national survey. Int J Epidemiol 8:333–338.

Melia RJW, Florey C du V, Morris RW, Goldstein BD, John HH, Clark D, Craighead IB, Mackinlay JC. 1982. Childhood respiratory illness and the home environment: II. Association between respiratory illness and nitrogen dioxide, temperature and relative humidity. Int J Epidemiol 11:164–169.

Meulenbelt J, Sangster B. 1990. Acute nitrous oxide intoxication: Clinical symptoms, pathophysiology and treatment. Neth J Med 37:132–138.

Miller FJ, Graham JA, Raub JA, Illing JW, Ménache MG, House DE, Gardner DE. 1987. Evaluating the toxicity of urban patterns of oxidant gases: II. Effects in mice from chronic exposure to nitrogen dioxide. J Toxicol Environ Health 21:99–112.

Mohsenin V. 1987. Airway responses to nitrogen dioxide in asthmatic subjects. J Toxicol Environ Health 22:371–380.

Mohsenin V. 1988. Airway responses to 2.0 ppm nitrogen dioxide in normal subjects. Am Rev Respir Dis 43:242–246.

Morgenstern H, Thomas D. 1993. Principles of study design in environmental epidemiology. Environ Health Perspect (in press).

National Academy Press. 1985. Epidemiology and Air Pollution. National Academy Press, Washington, DC.

National Research Council. 1991a. Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities. National Academy of Sciences, Washington, DC.

National Research Council. 1991b. Rethinking the Ozone Problem in Urban and Regional Air Pollution. National Academy Press, Washington, DC.

Neas LM, Dockery DW, Ware JH, Spengler JD, Speizer FE, Ferris BG Jr. 1991. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. Am J Epidemiol 134:204–219.

Ogston SA, Florey C du V, Walker CHM. 1985. The Tayside infant morbidity and mortality study: Effect on health of using gas for cooking. Br Med J (Clin Res Ed) 290:957–960.

Orehek J, Massari JP, Gayrard P, Grimaud C, Charpin J. 1976. Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J Clin Invest 57:301–307.

Palmes ED, Gunnison AF, DiMattio J, Tomczyk C. 1976. Personal sampler for nitrogen dioxide. Am Ind Hyg Assoc J 37:570–577.

Parker RF, Davis JK, Cassell GH, White H, Dziedzic D, Blalock DK, Thorp RB, Simecka JW. 1989. Short-term exposure to nitrogen dioxide enhances susceptibility to murine respiratory mycoplasmosis and decreases intrapulmonary killing of *Mycoplasma pulmonis*. Am Rev Respir Dis 140:502–512.

Pearlman ME, Finklea JF, Creason JP, Shy CM, Young MM, Horton JM. 1971. Nitrogen dioxide and lower respiratory illness. Pediatrics 47:391–398.

Pennington JE. 1988. Effects of automotive emissions on susceptibility to respiratory infections. In: Air Pollution,

the Automobile, and Public Health (Watson AY, Bates RR, Kennedy D, eds.) pp. 499–518. National Academy Press, Washington, DC.

Petreas M, Liu K-S, Chang B-H, Hayward SB, Sexton K. 1988. A survey of nitrogen dioxide levels measured inside mobile homes. J Air Pollut Control Assoc 38:647–651.

Ponka A. 1990. Absenteeism and respiratory disease among children and adults in Helsinki in relation to low-level air pollution and temperature. Environ Res 52:34–46.

Quackenboss JJ, Spengler JD, Kanarek MS, Letz R, Duffy CP. 1986. Personal exposure to nitrogen dioxide: Relationship to indoor/outdoor air quality and activity patterns. Environ Sci Technol 8:775–783.

Rombout PJA, Dormans JA, Marra M, van Esch GJ. 1986. Influence of exposure regimen on nitrogen dioxide–induced morphological changes in the rat lung. Environ Res 41:466–480.

Rose RM, Pinkston P, Skornik WA. 1989. Altered Susceptibility to Viral Respiratory Infection During Short-Term Exposure to Nitrogen Dioxide. Research Report Number 24. Health Effects Institute, Cambridge, MA.

Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. 1993. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399–405.

Rutishauser M, Ackermann U, Braun C, Gnehm HP, Wanner HU. 1990a. Significant association between outdoor NO_2 and respiratory symptoms in preschool children. Lung 168 (Suppl):347–352.

Rutishauser M, Ackermann U, Braun C, Gnehm HP, Wanner U. 1990b. Zusammenhang zwischen atemwegssymptomen bei kleinkindern und NO_2-konzentrationen in der aubenluft. Pneumologie 44:245–246.

Ryan PB, Hemphill CP, Billick IH, Nagda NL, Koontz MD, Fortmann RC. 1989. Estimation of nitrogen dioxide concentrations in homes equipped with unvented gas space heaters. Environ Int 15:551–556.

Ryan PB, Soczek ML, Traitmam RD, Spengler JD, Billick IH. 1988. The Boston residential NO_2 characterization study: II. Survey methodology and population concentration estimates. Atmos Environ 22:2115–2125.

Samet JM. 1991. Nitrogen dioxide. In: Indoor Air Pollution: A Health Perspective (Samet JM, Spengler JD, eds.) pp. 170–186. Johns Hopkins University Press, Baltimore, MD.

Samet JM, Cushing AH, Lambert WE, Hunt WC, McLaren LC, Young SA, Skipper BJ. 1993. Comparability of parent-reported respiratory illnesses to clinical diagnoses. Am Rev Respir Dis (in press).

Samet JM, Marbury MC, Spengler JD. 1987. Health effects and sources of indoor air pollution: Part I. Am Rev Respir Dis 136:1486–1508.

Samet JM, Spengler JD. 1989. Nitrogen Dioxide and Respiratory Infection: Pilot Investigations. Research Report Number 28. Health Effects Institute, Cambridge, MA.

Samet JM, Tager IB, Speizer FE. 1983. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am Rev Respir Dis 127:508–523.

Samet JM, Utell MJ. 1990. The risk of nitrogen dioxide: What have we learned from epidemiological and clinical studies? Toxicol Ind Health 6:247–262.

Schenker MB, Samet JM, Speizer FE. 1983. Risk factors for childhood respiratory disease: The effect of host factors and home environmental exposures. Am Rev Respir Dis 128: 1038–1043.

Schlesinger RB. 1987. Intermittent inhalation of nitrogen dioxide: Effects on rabbit alveolar macrophages. J Toxicol Environ Health 21:127–139.

Schwartz J, Hasselblad V, Pitcher H. 1988. Air pollution and morbidity: A further analysis of the Los Angeles student nurses data. J Air Pollut Control Assoc 38:158–162.

Schwartz J, Spix C, Wichmann HE, Malin E. 1991. Air pollution and acute respiratory illness in five German communities. Environ Res 56:1–14.

Schwartz J, Zeger S. 1990. Passive smoking, air pollution, and acute respiratory symptoms in a diary study of student nurses. Am Rev Respir Dis 141:62–67.

Science 1992. NO news is good news. Science 258:1862–1863.

Shy CM, Creason JP, Pearlman ME, McClain KE, Benson FB, Young MM. 1970. The Chattanooga school children study: Effects of community exposure to nitrogen dioxide: I. Methods, description of pollutant exposure, and results of ventilatory testing. J Air Pollut Control Assoc 20:539–545.

Shy CM, Creason JP, Pearlman ME, McClain KE, Benson FB, Young MM. 1970. The Chattanooga school children study: Effects of community exposure to nitrogen dioxide: II. Incidence of acute respiratory illness. J Air Pollut Control Assoc 20:582–588.

Speizer FE, Ferris BJ, Bishop YM, Spengler J. 1980. Respiratory disease rates and pulmonary function in children associated with NO_2 exposure. Am Rev Respir Dis 121:3–10.

Taussig LM, Wright AL, Morgan WJ, Harrison HR, Ray CG, The Group Health Medical Associates. 1989. The Tucson children's respiratory study: I. Design and implementation of a prospective study of acute and chronic respiratory illness in children. Am J Epidemiol 129:1219–1231.

Tepper JS, Costa DL, Winsett DW, Stevens MA, Doerfler DL, Watkinson WP. 1993. Near-lifetime exposure of the rat to a simulated urban profile of nitrogen dioxide: Pulmonary function evaluation. Fundam Appl Toxicol 20:88–96.

U.S. Environmental Protection Agency. 1991a. Air Quality Criteria for Oxides of Nitrogen: External Review Draft. EPA 600/8–91/049aA. Office of Research and Development, Washington, DC.

U.S. Environmental Protection Agency. 1991b. National Air Quality and Emissions Trends Report, 1990. EPA-450/4–91–023. Office of Air Quality Planning and Standards, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1992a. Aerometric Information Retrieval System (data base). Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1992b. Respiratory health effects of passive smoking: Lung cancers and other disorders. EPA-600/6–90–006F. Office of Research and Development, Washington, DC.

Utell MJ. 1989. Asthma and nitrogen dioxide: A review of the evidence. In: Susceptibility to Inhaled Pollutants (Utell MJ, Frank R, eds.) pp. 218–223. American Society for Testing Materials, Philadelphia, PA.

Utell MJ, Frampton MW, Roberts NJ Jr, Finkelstein JN, Cox C, Morrow PE. 1991. Mechanisms of Nitrogen Dioxide Toxicity in Humans. Research Report Number 43. Health Effects Institute, Cambridge, MA.

Ware JH, Dockery DW, Spiro A, Speizer FE, Ferris BG Jr. 1984. Passive smoking, gas cooking, and respiratory health of children living in six cities. Am Rev Respir Dis 129:366–374.

Warner PO, Stevens L. 1973. Revaluation of the "Chattanooga school children study" in the light of other contemporary governmental studies: The possible impact of these findings on the present NO_2 air quality standard. J Air Pollut Control Assoc 23:769–771.

Wilson AL, Colome SD, Baker PE, Becker EW. 1986. Residential indoor air quality characterization study of nitrogen dioxide: Phase I, Vol. 1, 2, and 3. Southern California Gas Co., Los Angeles, CA.

Wright AL, Holberg C, Martinez FD, Taussig LM, Group Health Medical Associates. 1991. Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. J Pediatr 118:207–214.

Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ, Group Health Medical Associates. 1989. The Tucson children's respiratory study: II. Lower respiratory tract illness in the first year of life. Am J Epidemiol 129:1232–1246.

Yockey CC, Eden BM, Byrd RB. 1980. The McConnell missile accident: Clinical spectrum of nitrogen dioxide exposure. JAMA 244:1221–1223.

Zeger SL, Liang KY. 1992. An overview of methods for the analysis of longitudinal data. Stat Med 11:1825–1839.

Zeger SL, Liang KY, Albert PS. 1988. Models for longitudinal data: A generalized estimating equation approach. Biometrics 44:1049–1060.

APPENDIX A. Some Representative Indoor Epidemiologic Studies of Nitrogen Dioxide and Respiratory Illness

Study	Exposure	Information Source and Outcomes	Findings	Reference
BRITISH STUDIES				
5,658 schoolchildren (6–11 years of age) in England and Scotland	Presence of gas stove	Self-administered parental questionnaire on respiratory symptoms (bronchitis, cough, colds going to chest, wheezing, asthma) in previous 12 months	Significant increase in all symptoms (except asthma) in boys and girls	Melia et al. 1977
4,827 schoolchildren (5–10 years of age) in England and Scotland	Presence of gas stove	Same as above	Small increase for some symptoms, but only significant for boys in urban areas when adjustments made	Melia et al. 1979
808 schoolchildren (6–7 years of age) in Middlesbrough, U.K.	Single one-week (indoor and outdoor) measurements of NO_2 in 515 homes (kitchens and bedrooms) during the winter	Same as above	Nonsignificant ($p \geq 0.10$) association of the prevalence of respiratory illness with cooking fuel and bedroom NO_2 levels ($n = 103$); positive trend ($p \geq 0.10$) reported for 80 children; no association with kitchen NO_2 levels ($n = 428$)	Florey et al. 1979; Goldstein et al. 1979
390 infants in London, U.K.	Presence of gas stove	Questionnaire on respiratory symptoms administered by a health professional when the child was 12 months of age; physician diagnosis	Nonsignificant decrease in prevalence of respiratory symptoms reported by mothers and those diagnosed by physician	Melia et al. 1983
1,565 infants (0–1 year of age) in Scotland	Presence of gas stove or gas heater	Hospitalization for respiratory illness; questionnaire on respiratory illness administered by a health professional when the child was 12 months of age	No significant association of either outcome with cooking or heating fuel	Ogston et al. 1985
U.S. STUDIES				
1,355 schoolchildren (6–12 years of age) in Iowa City, IA	Presence of gas stove	Parental questionnaire about hospitalization and respiratory symptoms (chest congestion without phlegm, wheezing without colds); time period not stated	Positive association of gas cooking with hospitalization for respiratory illness before 2 years of age; no association with symptoms in the preceding year	Ekwo et al. 1983
1,205 healthy infants (0–18 months) in Albuquerque, NM	Consecutive two-week measurements of NO_2 in homes with gas stoves; alternate two-week measurements of NO_2 in homes with electric stoves	Daily parental diary of incidence and duration of respiratory illness with surveillance at two-week intervals by a health professional; symptoms classified as upper respiratory illness or lower respiratory illness (at least one day of wet cough or wheezing); supplemented by clinical evaluation	No association of bedroom NO_2 levels with incidence of respiratory illness or duration of upper respiratory illness, lower respiratory illness, and lower respiratory illness with wet cough; nonsignificant increase in lower respiratory illness with wheezing	Samet et al. 1993

(Appendix A continues next page.)

APPENDIX A. (*continued*)

Study	Exposure	Information Source and Outcomes	Findings	Reference
U.S. SIX CITIES STUDIES				
8,866 children (6–10 years of age at time of initial survey) in six U.S. cities (Kingston/Harriman, TN; Portage, WI; St. Louis, MO; Steubenville/Mingo Junction, OH; Topeka, KS; Watertown, MA)	Presence of gas stove	Parental questionnaire at time of entry into study on respiratory symptoms (history of physician-diagnosed bronchitis, history of respiratory disease prior to two years of age, history of respiratory illness in last year)	Marginally significant increase in history of respiratory disease before two years of age; no effect on other end points	Speizer et al. 1980
Analysis of complete cohort of 10,106 children	Presence of gas stove	Same as above, plus additional symptoms (bronchitis, persistent cough, wheezing); used data from two annual questionnaires	No association of respiratory illness in the preceding year with the presence of gas stoves; small increase in the incidence of respiratory symptoms before two years of age (not significant when adjusted for socioeconomic status)	Ware et al. 1984
New cohort of 1,567 children (7–11 years of age)	Two one-week measurements of NO_2, or one two-week measurement of NO_2 at three locations in subjects' homes in summer and winter and winter	Parental questionnaire on the prevalence of lower respiratory symptoms (shortness of breath with wheezing, persistent wheezing, chronic cough, chronic phlegm, bronchitis, physician-diagnosed asthma) in the preceding year	Odds ratios for 9 of 11 symptoms were elevated, but only significant for the combined lower respiratory symptoms category (odds ratio = 1.4; 95% CI 1.1, 1.7); odds ratio increased monotonically with increasing NO_2 levels	Neas et al. 1991
NORTHERN EUROPEAN STUDIES				
1,051 schoolchildren (6–12 years of age) in the Netherlands	Single one-week measurements of NO_2 (living rooms, kitchens, and bedrooms) in winter; NO_2 source was gas-fired hot water heaters	Self-administered parental questionnaire on upper respiratory symptoms (cough, wheeze, asthma)	No relationship between indoor NO_2 levels and upper respiratory tract symptoms	Dijkstra et al. 1990
1,225 children (0–5 years of age) in urban, surburban, and rural areas of Switzerland	Six one-week measurements of NO_2 (outside, bedrooms, personal) in all seasons	Daily parental diary of respiratory symptoms (cough, runny nose, fever, earache)	Significant relationship between outdoor (but not indoor) NO_2 and incidence of upper respiratory illness as determined by combined respiratory symptoms; outdoor NO_2 concentrations were higher than indoor levels	Braun-Fahrländer et al. 1989; Rutishauser et al. 1990a,b
625 children (0–5 years of age) in same locations given above	Same as above, plus measurements of outdoor total suspended particulates and sulfur dioxide	Same as above; 20% of the diaries validated by a physician	No association of indoor NO_2 levels with any outcome; marginally significant association of outdoor NO_2 with duration; total suspended particulate levels were stronger predictors of illness duration	Braun-Fahrländer et al. 1992

APPENDIX B. Selected Air Quality Standards and Recommended Limits for Nitrogen Dioxide

Location or Source	NO_2 Concentration (ppb)	Method of Calculation
Ambient Levels		
California	250	One-hour average
European Community	106	One-hour average
Germany	106	0.5-Hour average
	53	24-Hour average
Japan	40–60	24-Hour average
United States	53	Annual arithmetic mean
World Health Organization	212	One-hour average
	80	24-Hour average
Occupational Levels		
U.S. National Institute of Occupational Safety and Health	5,000	15-Minute average
U.S. Occupational Safety and Health Administration	1,000	15-Minute average

APPENDIX C. The Health Effects Institute Research and Review Process

In 1983, the Health Effects Institute issued a Request for Applications, RFA 83–4, that requested applications for "Epidemiologic Investigation of Effects of Automotive Emissions." One of the objectives of this RFA was to investigate the effects of nitrogen oxides on susceptibility to respiratory infections. The Research Committee also requested proposals to test the same hypothesis in other experimental models by issuing RFA 83–2 "Nitrogen Oxides and Susceptibility to Respiratory Infections." In response to RFA 83–4, Dr. Jonathan Samet of the School of Medicine at the University of New Mexico, and Dr. John Spengler of the Harvard School of Public Health, submitted an application for an epidemiologic study entitled "Nitrogen Oxides and Respiratory Infection in Infants."

Before undertaking a full study, the HEI Research Committee asked the investigators to conduct two pilot studies to develop and assess their proposed methods. The specific aims of these studies were:

1. To document that sufficient numbers of infants meeting the eligibility criteria for the proposed cohort study could be identified and enrolled;
2. To describe the distribution of nitrogen dioxide concentrations in homes in Albuquerque, NM, with gas stoves and in homes with electric stoves;
3. To measure potentially confounding pollutants in homes sampled from the upper and lower tails of the distribution of nitrogen dioxide levels;
4. To develop approaches for establishing the personal exposures of infants to nitrogen dioxide;
5. To conduct a pilot test of the proposed surveillance methods for monitoring respiratory illnesses; and
6. To develop and test methods for data analysis.

The first pilot study began in September 1984; the second study began in February 1986. Total expenditures for the two pilot studies were $283,328. The results were reported in HEI Research Report Number 28 (Samet and Spengler 1989).

The full study, which is the subject of this report, began in April 1987. The projected costs are $3.43 million. In addition to support from HEI's regular sponsors, funding for Dr. Samet's project was also provided by the Gas Research Institute, which supported one third of the research costs. Recruitment of subjects began in December 1987, and data collection was completed in December 1991. Before recruitment began, the HEI Research Committee appointed an Advisory Committee to work with the HEI staff and expert consultants to develop a comprehensive oversight plan. Members of the Advisory Committee are listed in Table C.1.

The involvement and cooperation of the local medical community was a key factor in the success of the project. In order to engage the interest and support of local physicians who would be a source of subjects for the study, HEI sponsored a conference, "Childhood Respiratory Infections and the Environment," at the University of New Mexico on October 23, 1987. The conference was preceded by a full-day meeting of consultants to the study to discuss classification of respiratory illnesses.

Upon completion of any study funded by HEI, the investigators submit a final report on the work, which undergoes a detailed evaluation by the Institute's Health Review Committee. Because of the complexity of Dr. Samet's study and

Table C.1. Study Participants

Field Study
University of New Mexico: J.M. Samet, W.E. Lambert, B.J. Skipper, A.H. Cushing, W.C. Hunt, S.A. Young, and L.C. McLaren. Harvard School of Public Health: J.D. Spengler and M. Schwab.

Nitrogen Dioxide Exposures
Harvard School of Public Health: J.D. Spengler and M. Schwab. University of New Mexico: W.E. Lambert, J.M. Samet, W.C. Hunt, and B.J. Skipper

Quality Assurance
Arthur D. Little, Inc.: D. Hayes

Advisory Committee
HEI Research Committee: M.J. Utell (chair), L. Gordis, R.O. McClellan, R.L. Prentice, R. Remington, and J.W. Tukey

Project Managers
HEI staff: A.J. Cohen, P.L. Kinney, and J. Warren

its importance for the regulatory process, the Health Review Committee appointed a Technical Review Panel (Table C.2), composed of epidemiologists, pediatricians, biostatisticians, and environmental scientists, to assist the Committee in the evaluation of the study.

In June 1992, Dr. Samet submitted two draft reports and three appendices to HEI:

- Draft Investigators' Report Number 1: Nitrogen Dioxide and Respiratory Infection in Children by JM Samet, WE Lambert, BJ Skipper, AH Cushing, WC Hunt, SA Young, LC McLaren, M Schwab, JD Spengler.
- Draft Investigators' Report Number 2: Characterization of Infants' Residential Exposures to Nitrogen Dioxide by WE Lambert, JM Samet, WC Hunt, BJ Skipper, M Schwab, JD Spengler.
- Appendix Number 1: A Study of Respiratory Illness in Infants and Nitrogen Dioxide Exposure (project overview) by JM Samet, WE Lambert, BJ Skipper, AH Cushing, LC McLaren, M Schwab, JD Spengler. 1992. Arch Environ Health 47:57–63.
- Appendix Number 2: Comparability of Parent Reports of Respiratory Illnesses with Clinical Diagnoses in Infants (information on diagnostic criteria) by JM Samet, AH Cushing, WE Lambert, WC Hunt, LC McLaren, SA Young, BJ Skipper.
- Appendix Number 3: The Risk of Nitrogen Dioxide: What Have We Learned From Epidemiological and Clinical Studies (general background)? by JM Samet, MJ Utell. 1990. Toxicol Ind Health 6:247–262.

The Technical Review Panel met with the principal investigators (Drs. Samet and Spengler) in July 1992 to review and discuss the draft Investigators' Reports. After the meeting, the panel members' critiques and the HEI Initial Review were sent to the investigators, who responded to the panels' comments and provided revised reports in October 1992. The revised reports and the investigators' response were sent to the members of the Panel for comment and dis-

Table C.2. Technical Review Panel

Arthur Upton[a] (co-chair)
New York University (until December 1992)

Bernard Goldstein[b] (co-chair)
Environmental and Occupational Health Sciences Institute

Ralph B. D'Agostino
Boston University

A. Sonia Buist[c]
Oregon Health Sciences University

Albert M. Collier
University of North Carolina School of Medicine

Millicent W.P. Higgins
National Heart, Lung and Blood Institute

Fernando D. Martinez
University of Arizona

Arthur M. Winer
UCLA School of Public Health

[a] Also Chairman of the HEI Review Committee during the review of this study.

[b] Also a member of the HEI Review Committee until August 1992.

[c] Also a member of the HEI Review Committee.

cussed by the HEI Health Review Committee in November 1992.

A draft of this Commentary was circulated to the investigators, as well as to members of the HEI Advisory Committee, for their information and comment. After appropriate revisions and approval by the HEI Health Review Committee, the Investigators' Reports and the Health Review Committee's Commentary were sent to the HEI Board of Directors with a strong endorsement of the study and a recommendation to publish the report in the HEI Research Report series.

RELATED HEI PUBLICATIONS: NITROGEN DIOXIDE

Research Reports

Report No.	Title	Principal Investigator	Publication Date
Biological Mechanisms and Dose to Target Tissues			
1	Estimation of Risk of Glucose 6-Phosphate Dehydrogenase-Deficient Red Cells to Ozone and Nitrogen Dioxide	M.A. Amoruso	August 1985
3	Transport of Macromolecules and Particles at Target Sites for Deposition of Air Pollutants	T. Crocker	February 1986
6	Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate on Metabolic and Pulmonary Function	D.M. Drechsler-Parks	April 1987
8	Effects of Inhaled Nitrogen Dioxide and Diesel Exhaust on Developing Lung	J.L. Mauderly	May 1987
9	Biochemical and Metabolic Response to Nitrogen Dioxide–Induced Endothelial Injury	J.M. Patel	June 1987
11	Effects of Ozone and Nitrogen Dioxide on Human Lung Proteinase Inhibitors	D.A. Johnson	August 1987
13	Effects of Nitrogen Dioxide on Alveolar Epithelial Barrier Properties	E.D. Crandall	October 1987
14	The Effects of Ozone and Nitrogen Dioxide on Lung Function in Healthy and Asthmatic Adolescents	J.Q. Koenig	January 1988
23	Responses of Susceptible Subpopulations to Nitrogen Dioxide	P.E. Morrow	February 1989
26	Investigation of a Potential Cotumorigenic Effect of the Dioxides of Nitrogen and Sulfur, and of Diesel-Engine Exhaust, on the Respiratory Tract of Syrian Golden Hamsters	U. Mohr (U. Heinrich)	May 1989
29	Early Markers of Lung Injury	J.N. Evans	September 1989
30	Influence of Experimental Pulmonary Emphysema on Toxicological Effects from Inhaled Nitrogen Dioxide and Diesel Exhaust	J.L. Mauderly	October 1989
37	Oxidant Effects on Rat and Human Lung Proteinase Inhibitors	D.A. Johnson	December 1990
43	Mechanisms of Nitrogen Dioxide Toxicity in Humans	M.J. Utell	August 1991
45	The Effects of Exercise on Dose and Dose Distribution of Inhaled Automotive Pollutants	M.T. Kleinman	October 1991
Respiratory Disease			
15	Susceptibility to Virus Infection with Exposure to Nitrogen Dioxide	T.J. Kulle	January 1988
18	Respiratory Infections in Coal Miners Exposed to Nitrogen Oxides	M. Jacobson	July 1988
20	Modulation of Pulmonary Defense Mechanisms Against Viral and Bacterial Infections by Acute Exposures to Nitrogen Dioxide	G.J. Jakab	October 1988
24	Altered Susceptibility to Viral Respiratory Infection During Short-Term Exposure to Nitrogen Dioxide	R.M Rose	March 1989
28	Nitrogen Dioxide and Respiratory Infection: Pilot Investigations	J.M. Samet	September 1989
43	Mechanisms of Nitrogen Dioxide Toxicity in Humans	M.J. Utell	August 1991
47	Murine Respiratory Mycoplasmosis: A Model to Study Effects of Oxidants	J.K. Davis	December 1991

Copies of these reports can be obtained by writing or calling the Health Effects Institute, 141 Portland Street, Suite 7300, Cambridge, MA 02139. Phone 617 621-0266. FAX 617 621-0267. Request a Publications and Documents booklet for a complete listing of publications resulting from HEI-sponsored research.

HEI

HEALTH EFFECTS INSTITUTE

141 Portland Street, Cambridge, MA 02139 (617) 621-0266

Research Report Number 58

June 1993