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Nitrogen Dioxide and Respiratory Infection: Pilot Investigations

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Includes the Commentary by the Institute's Health Review Committee

Research Report Number 28

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HEALTH REVIEW COMMITTEE'S COMMENTARY Health Effects Institute

Nitrogen Dioxide and Respiratory Infection: Pilot Investigations

Jonathan M. Samet[1] and John D. Spengler

ABSTRACT

Laboratory and human studies have raised concern that exposure to nitrogen dioxide may increase the frequency and severity of respiratory infections in children and adults. Cooking with a natural-gas-fueled stove exposes a home's residents to short-term peaks of nitrogen oxides and to higher average levels of nitrogen oxides than are measured in homes with electric stoves. We have designed a longitudinal study of infants to determine if nitrogen dioxide exposure from cooking stoves increases the incidence or severity of respiratory infections during the first 18 months of life. Pilot investigations for the longitudinal study were conducted from 1984 through 1986. This report provides the results of the pilot investigations.

The first study, conducted in 1984 and 1985, was designed to document (1) that appropriate subjects could be recruited; (2) that nitrogen dioxide concentrations in Albuquerque homes were in the range of interest; (3) that an infant's personal exposure to nitrogen dioxide could be estimated; and (4) that a valid, feasible approach for surveillance could be implemented. To accomplish these goals, the families of infants were recruited at two Albuquerque hospitals, and their homes were monitored for nitrogen dioxide using a passive sampling tube. With this approach, we successfully recruited 147 households; monitoring for nitrogen dioxide showed substantially higher levels in homes with gas stoves than in homes with electric stoves, as previously found in other U.S. cities. More detailed investigations in a sample of the homes showed that personal exposures of the infants, who did not attend day care, could be satisfactorily estimated by room concentrations. We also demonstrated that mothers would complete a daily calendar-diary on respiratory symptoms and provide information every two weeks on illnesses occurring since the previous surveillance call.

The second pilot study, conducted in 1986, was designed to refine the system for illness surveillance. Additional goals were to test further the methods for exposure assessment and to evaluate recruitment of subjects through pediatric practices. We recruited 75 infants and followed them over a four-month period. Information from the surveillance system was compared with the clinical assessments of the project's nurse practitioner and the subjects' physicians, and with the results of viral cultures. We also evaluated biweekly versus weekly surveillance calls. Overall, the results of the second pilot study documented that a surveillance system for respiratory illness that incorporates calendar-diaries and biweekly telephone calls is a feasible, relatively unbiased, and sensitive method for studying respiratory illness in a large population of infants. We also found that subjects could be successfully recruited through a pediatric practice.

The findings of these two pilot investigations guided the development of the longitudinal study, which is now in progress. The findings of the pilot studies led to strategies for accurately measuring health outcomes and exposure to nitrogen dioxide.

INTRODUCTION

Defense mechanisms of the lung against infectious agents include aerodynamic filtration, mucociliary transport, phagocytosis and killing by alveolar macrophages, and local and systemic immune responses (Green et al. 1977). In experimental models, nitrogen dioxide (NO_2) reduces the efficacy of several of these lung defense mechanisms; effects on mucociliary clearance, the alveolar macrophage, and the immune system have been demonstrated (National Research Council 1976; Dawson and Schenker 1979; Morrow 1984). (The results of some experimental models, however, have not implied adverse effects of NO_2 on lung defenses [Lefkowitz et al. 1986; Mochitate et al. 1986].)

In animal experiments involving challenge with respiratory pathogens, exposure to NO_2 reduces clearance of the infecting organisms and increases the mortality of the experimental animals (National Research Council 1976; Dawson and Schenker 1979; Jakab 1980; Morrow 1984). In these infectivity models, the pathogens have most often been bacteria, although viruses have also been used (Morrow 1984). The viral exposure studies have generally, but not uniformly, suggested an adverse effect of NO_2 on the outcome of infection (Buckley and Loosli 1969; Henry et al. 1970; Fenters et al. 1973; National Research Council 1976).

The findings of these laboratory studies have raised concern that exposure to NO_2 may increase the frequency and

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the severity of respiratory infections in children and adults. The relevant epidemiological data are conflicting, however, in spite of several decades of research directed at this pollutant. Few investigations directed at NO_2 exposure from ambient sources have involved populations exposed primarily to NO_2 (National Research Council 1976). More often, the NO_2 has been a component of a complex pollutant mixture and the effects of exposure could not be attributed to NO_2 alone. Studies of occupationally exposed individuals have the same potential limitation. Thus, the results of community studies, such as those conducted by the U.S. Environmental Protection Agency in Chattanooga, TN (Shy et al. 1970), cannot satisfactorily test whether or not exposure to NO_2 increases the occurrence or severity of respiratory infections.

During the 1970s, it was recognized that cooking with a natural-gas-fueled stove exposed a home's residents to short-term peaks of nitrogen oxides and to higher average levels of nitrogen oxides than were found in homes with electric stoves (National Research Council 1981). The combustion process releases NO_2 and nitric oxide; concentrations are highest in the kitchen but are also increased in other rooms in a home (Yocom 1982). Consequently, measured personal exposures to NO_2 are higher for individuals from homes with gas stoves than for those from homes with electric stoves (Quackenboss et al. 1982; Yocom 1982; Spengler et al. 1983). Thus, within communities with low levels of ambient NO_2, stove type will determine personal exposure to NO_2 for most persons, and the resulting gradient of NO_2 exposures provides an opportunity for research on the health effects of NO_2.

The available epidemiological literature provides conflicting evidence concerning the health effects of exposure to emissions from gas stoves in children and adults (Samet et al. 1987). In most of the investigations of gas stoves and respiratory illnesses, schoolchildren have been the study subjects (Melia et al. 1977, 1979; Florey et al. 1979; Keller et al. 1979a,b; Speizer et al. 1980; Schenker et al. 1983; Ware et al. 1984; Ogston et al. 1985), but adults have also been investigated (Samet et al. 1987). The results of these investigations are conflicting; nevertheless, the uncertainties introduced by methodological limitations of the investigations must be considered. In most of the investigations of children, illness histories have been obtained retrospectively by parent-completed questionnaires, an approach that is inaccurate and potentially biased (Samet et al. 1983). The infecting agents were not adequately characterized in any of the investigations. Although NO_2 levels were directly measured in a few of the investigations (Florey et al. 1979; Keller et al. 1979a; Melia et al. 1982), exposure was usually assessed by simple questions concerning type of cooking stove. However, personal exposures to NO_2 are not adequately predicted by categorical descriptions of sources; use of stove type to estimate exposure would be expected to introduce misclassification and lead to underestimation of the true effect of exposure (Ozkaynak et al. 1984).

In summary, exposure to NO_2 from gas stoves has not been established as a risk factor for respiratory tract infection in humans. However, the investigations to date have substantial methodological limitations, and only two have included infants as study subjects (Melia et al. 1983; Ogston et al. 1985). Consideration of the evidence on involuntary smoking suggests that infants, and not schoolchildren or adults, are the most suitable subjects for an investigation of gas stoves and respiratory tract infection. The incidence of respiratory infection, and, specifically, of lower respiratory tract infection, is highest during the first year of life (Glezen and Denny 1973; Monto and Ullman 1974), and passive exposure to tobacco smoke appears to have the largest effect on the incidence of lower respiratory tract infection during the first year of life (U.S. Department of Health and Human Services 1986). The time-activity patterns of infants generally make the home environment the predominant source of exposure to NO_2. Detailed monitoring of indoor and outdoor NO_2 concentrations further indicates that simple categorical descriptors of exposure, based on NO_2 sources alone, are not satisfactory.

AIMS

In 1983, we submitted a response to Request for Applications 83–2 from the Health Effects Institute, "Nitrogen Oxides and Susceptibility to Respiratory Infections." In our response, we proposed to conduct a cohort study of respiratory illness during the first year of life in relationship to NO_2 exposure. We considered that this design would address many of the deficiencies of previous studies of NO_2 and respiratory illness. The design incorporated measurements of exposure, detailed assessment of potential confounding factors, and carefully standardized ascertainment of illness. Furthermore, we felt that it was important to study infants because, as stated earlier, infants have the highest incidence of respiratory infection, and they may be more susceptible to the effects of inhaled pollutants than older children and adults. For those infants not attending day care outside of the home, personal exposures to NO_2 are largely determined by sources in the home.

This proposal was not funded, but, in collaboration with the Research Committee of the Health Effects Institute, we planned and conducted a series of pilot investigations from 1984 through 1986. These investigations were designed to address questions concerning the feasibility and methodology of the proposed cohort study. The chronology, methods, and aims of the two sets of pilot studies are described in Table 1. The methods and results of the two pilot studies will be described separately in this report.

FIRST PILOT STUDY

METHODS

This pilot study had multiple aims (Table 1) that were met by data collected in three phases. We will present the methods and results separately for each phase.

Phase 1

In the first phase, we identified infants for the study, obtained the cooperation of their parents, and monitored their homes for two two-week periods during November and December 1984. Screening for eligible infants was accomplished by direct personal contact on the postpartum wards at the University of New Mexico Hospital and Lovelace Medical Center, and by telephone contact with mothers who had delivered before the study began. The latter approach was used to ensure a sufficient number of infants for the project.

The labor and delivery logs at both the University of New Mexico Hospital and Lovelace Medical Center were reviewed each day. The names and ages of women who had given birth in the previous 24 hours were abstracted onto the screening form. The log was also scanned for indications of any complications or problems with the infant. Initially, staffing permitted the collection of information only on weekdays. All days of the week were covered beginning in mid-October. Screening started on September 17, 1984, at the University of New Mexico Hospital, and on October 1, 1984, at Lovelace Medical Center, and was completed on November 19, 1984, at both institutions.

For each birth ascertained from the log, postpartum records were checked for problems with the mother's or infant's health, and for maternal fluency in English. Women who were under age 18, whose baby was placed in the intensive care unit or had a congenital defect, who did not speak English, or who had already left the hospital were not interviewed. Infants of mothers who smoke and infants from households with other adult smokers were also excluded. Rarely, a woman not yet discharged could not be located.

For the telephone screening, names of women who had delivered between July and September were ascertained from the labor and delivery logs. The logs were scanned for indications of complications, and all names were checked against the log of the neonatal intensive care unit. Women who were under 18 years of age or whose babies were in the intensive care unit were removed from the list. The patient's telephone number was then obtained from the admissions office. Women who did not have a phone or who lived outside the study area were excluded from the list. In contrast to the hospital screening procedure, no form was filled out

Table 1. Chronology and Aims of the First and Second Pilot Investigations

First Pilot Investigation (September 1984 – April 1985)	Second Pilot Investigation (January 1986 – July 1986)
Phase 1	
1. Document that sufficient numbers of infants meeting the eligibility criteria for the proposed cohort study could be identified and enrolled.	1. Evaluate recruitment of infants through a pediatrician's office.
2. Describe the distribution of NO_2 concentrations in Albuquerque homes with gas stoves and those with electric stoves.	2. Refine the system for surveillance of respiratory illnesses.
Phase 2	3. Further evaluate and refine the methodology for monitoring NO_2.
3. Measure potentially confounding pollutants in homes sampled from the upper and lower tails of the distribution of NO_2 levels	4. Develop and test methods for data analysis.
4. Develop approaches for establishing the personal exposures of infants to NO_2.	
Phase 3	
5. Pilot test a system for surveillance of respiratory illnesses.	

for women excluded from the list. We attempted to call everyone on the list of eligible homes. If the parents lived outside Albuquerque, or the phone number was not for their own homes, no further attempts were made to contact them. During the screening call, information was collected to determine the infant's eligibility.

For each participating infant's home, a housing-characteristics questionnaire was completed and NO_2 concentrations were monitored for two consecutive two-week periods. Palmes tubes, passive monitoring devices for NO_2 (Palmes et al. 1976), were placed in 147 homes for two weeks between November 12 and November 30, and were replaced two weeks later for another two-week cycle. The infant's bedroom and the family's principal activity room were monitored during the two periods; outdoor levels were obtained only once. Complete data were obtained on two-week NO_2 levels for 144 homes (98 percent of the initial study subjects), and on month-long NO_2 levels for 134 homes (91.2 percent).

Phase 2

The principal objective was to determine if levels of potentially confounding exposures varied systematically with NO_2 levels. Other objectives were to investigate spatial and temporal patterns of NO_2 concentrations, to test procedures for examining time-activity patterns of infants, and to assess different approaches for estimating the personal exposure of an infant to NO_2. Data collection for this phase began January 26, 1985, and ran through March 17, 1985.

We picked 50 homes from the initial group of 147: 25 homes from the upper quartile of activity-room NO_2 concentration, and 25 from the lower quartile. Four households from each group refused further participation. When a household refused, another was selected from the list. In addition, indoor and outdoor air at the homes of two staff members were monitored during this period to obtain information on outdoor NO_2 levels and the penetration of particles into the homes.

On the initial visit to each home, the field technician set up monitors for one-week determinations of water vapor, respirable particles, air-exchange rates, and NO_2. Week-long water-vapor measurements were taken in all homes, using a diffusion sampling tube modified from the Lawrence Berkeley Laboratory design (Girman et al. 1984). These measurements were made in the family's principal activity room.

The particulate samples were collected for one week in the activity room with a low-flow-rate impactor designed for indoor air sampling (Marple et al. 1987). The impactors operated at a flow rate of 4 lpm and collected particles of less than 2.5 μm in aerodynamic diameter. A total air volume of approximately 40 m^3 was sampled in each home. To correct for altitude, the sampler flow rate was recalibrated in Albuquerque using a National Bureau of Standards traceable bubble meter (Teledyne Hastings-Raydist, Hampton, VA). At set-up and pick-up of the impactor, the flow range was checked with a calibrated rotameter (Matheson Gas Products, East Rutherford, NJ). A built-in timer was set for a week-long sampling period, and total elapsed time was recorded at set-up and pick-up. Particles less than 2.5 μm were collected on a preweighed Teflon filter, Ghia XXX (Gelman Sciences Inc., Ann Arbor, MI), 2-μm pore size. Filters were subsequently reweighed on the same Cahn 21 (Cahn Instruments Inc., Cerritos, CA) electro-balance after 48 hours of conditioning in a temperature- and humidity-controlled room. Net mass gain was corrected for zero drift, as indicated by laboratory filter blank changes. X-ray fluorescence spectrometry was used to analyze the particulate samples for component elements (Schroeder et al. 1987).

One-week duration samples for particles were collected at five outdoor locations. The sites were chosen to be representative of Albuquerque, in terms of both geography and traffic density. The five sites were sampled in sequence, and monitoring was continuous throughout the entire Phase 2 period.

Palmes tubes (Palmes et al. 1976) were used for the NO_2 measurements. The tubes were placed in the kitchen, primary activity room, infant's bedroom, and outdoors at all homes. In gas-stove homes, samplers were also placed on the ceiling directly over the gas range. To characterize day-to-day variation of NO_2 concentrations, eight households were enrolled in a special study that involved seven serial one-day measurements. Yanagisawa filter badges for NO_2 (Yanagisawa and Nishimura 1982) were placed in the activity room and changed daily.

Average air-exchange rates during the one-week period were measured with a perfluorocarbon tracer system developed by Brookhaven National Laboratories (Dietz et al. 1986) and subsequently modified by the Harvard Air Quality Group. Two separate perfluorocarbon tracers, perfluoromethylcyclohexane (PMCH) and perfluorodimethylcyclohexane (PDCH), were used; three emitters of one perfluorocarbon tracer were placed in the kitchen, and emitters of the other perfluorocarbon tracer were placed in three other rooms around the home. Capillary absorption tubes, which passively absorb the tracers, were placed in three rooms of the home. The concentrations of tracer gas in the capillary absorption tubes were determined by gas chromatographic analysis.

Whole-house air-exchange rates were calculated by using a simple mass-balance equation. The concentration of either PMCH or PDCH is given by the quotient of the source term with the product of airflow rate through the home and the volume of the structure so that the air-exchange rate (a) can be calculated by $a = s/cv$, where s is the source strength, c is the measured concentration, and v is the house volume. The volume was directly measured, and the source strength of the emitters was determined in the laboratory by measuring the weight loss over time. Airflow rate was then calculated from the mass-balance equation. The whole-house air-exchange rate was obtained by dividing the house volume by the airflow rate. With a one-week averaging time, the assumption of a steady state with adequate air mixing can be justified.

With this approach, separate measures of whole-house air exchange can be derived on the basis of the two separate perfluorocarbon tracers and the multiple capillary absorption tubes that were deployed. For this report, we have averaged the four whole-house air-exchange rates that can be calculated using the kitchen and bedroom absorption tubes and the two tracers. This approach provides a more stable estimate of the whole-house air-exchange rate than would be given by any one of the four separate values.

Because the emission rates of the perfluorocarbon sources are temperature-dependent, the air-exchange rates were corrected for house temperature during the period of measurement. We used the average of the weekly maximum and minimum temperatures for this correction.

Eleven homes were also sampled for formaldehyde. Initially, we planned to measure formaldehyde in all homes, but because of a limited supply of samplers, we were able to monitor only a sample of the homes. Week-long formaldehyde concentrations were measured in the activity room using the Air Quality Research, Inc. (Berkeley, CA) passive diffusion tube.

During the initial visit to the home for placement of the monitors, the field technician arranged a return visit for one morning during the following seven days. On this second visit, the technician administered a questionnaire, took photographs to document sampler locations, made house-volume measurements, and instructed the mother on completing a 24-hour time-activity form. At homes from the high end of the NO_2 distribution, the technician also placed Yanagisawa filter badges (Yanagisawa and Nishimura 1982) in the kitchen, activity room, and bedroom, and on the infant. The technician instructed the mother to put the badges into a mason jar and to seal it tightly at bedtime to stop sampling and prevent contamination of the badges. The technician also placed on the stove a small portable pump attached to a prototype cartridge sampling device for NO_2. The mother was instructed to turn on the pump when she was cooking and to turn it off 30 minutes after she stopped.

Time-activity logs were completed for each infant by recording the predominant location of the infant during each half-hour period of the day. We used seven location categories for which we measured or could estimate NO_2 levels for the 24-hour activity period. On the day of the technician's visit for the short-term monitoring of gas-stove homes, a retrospective log was recorded for the previous 24 hours and a log was left for prospective completion during the current 24-hour period.

Phase 3

The overall objective was to pilot test the illness surveillance methodology that had been proposed for the cohort study and to validate the surveillance system against conventional clinical criteria. This task was to be accomplished during a three-month period (February 20 through May 1985) with subjects not included in Phase 2, because we did not want to place excessive demands on families by asking for participation in both Phases 2 and 3.

We contacted 83 Phase 1 families to enroll 53 infants. Reasons for nonparticipation were as follows: moved ($n = 5$); returned to work ($n = 4$); telephone disconnected ($n = 3$); baby deceased ($n = 1$); refused ($n = 12$); and unable to contact ($n = 5$). The nurse practitioner visited each family that agreed to participate, and explained the surveillance procedures. Each mother was asked to complete a daily calendar for the symptom status of her child. The symptoms were chosen on the basis of discussion with local pediatricians, and by review of similar forms used in the Tecumseh and East Boston studies (Monto and Cavalaro 1971; Tager and Speizer 1976). The mother was also asked to write the names of any ill family members on the calendar. Approximately every two weeks, the nurse practitioner made a telephone surveillance call to the household and completed a standard series of questions if the child had been ill. Mothers were also given postcards to be completed by their pediatricians at the time of any visits for illness. The postcards requested the patient's name, date of visit, and the diagnosis. In addition, each mother was asked to contact the study office if her child became ill. Finally, the nurse practitioner attempted to visit all children when ill and on at least one occasion when healthy. At these visits, the child was assessed according to a standardized examination protocol. Nasopharyngeal swabs were obtained for viral fluorescent antibody stains at 100 of the 107 visits.

RESULTS

Phase 1

We screened 611 women in the hospital on the postpartum wards. Of these, 437 (72 percent) were interviewed, and 166 (27 percent) were eligible. Of the 270 births in the telephone screening pool, 155 (56 percent) of the mothers were interviewed, and 88 (32 percent) were eligible. Of the women who were eligible, only six of the hospital group (3.6 percent) and four of the telephone group (4.6 percent) initially refused to participate. Table 2 lists the reasons for ineligibility.

The characteristics of the mothers, by eligibility and participation status, are described in Table 3. Refusals occurred at initial screening ($n = 10$) or at first contact to schedule an appointment ($n = 36$). We also lost eligible candidates because they had moved or their telephones had been disconnected ($n = 21$), they had become ineligible ($n = 32$), or final arrangements could not be made for a visit ($n = 11$). The proportion of eligible births varied with hospital, maternal age, ethnicity, and family size, but not with stove type (Table 3). These same factors also influenced participation rates.

Initially, we compared the responses to the household-characteristics questionnaire for the homes with gas stoves and those with electric stoves (Table 4). The households with electric stoves had a higher annual household income on average; the homes with electric stoves more often had multiple bathrooms and were more often heated by a central furnace. While incomes differed in the two groups, the parents' educational levels were similar.

Outdoor concentrations of NO_2 exceeded those indoors in electric-stove homes, whereas the opposite pattern was observed in gas-stove homes (Table 5). Outdoor levels at gas-stove homes were somewhat higher than outdoor levels at electric-stove homes. This finding may reflect random variation in outdoor levels or a greater concentration of electric-stove homes in areas with lower ambient air NO_2 levels. The outdoor levels increased over the sampling period (Figure 1) in a fashion consistent with the Albuquerque climate; nighttime inversions begin in early December, resulting in an increase in ambient pollution levels.

Histograms showing the distribution of NO_2 levels in the activity rooms and infants' bedrooms in each cycle are shown in Figures 2 through 5. Most electric-stove homes had concentrations below 20 parts per billion (ppb) in both rooms. In contrast, 20 to 30 percent of the two-week measurements in the activity room and 14 to 16 percent of the two-week measurements in the bedroom in gas-stove homes exceeded the current National Ambient Air Quality Standard for NO_2 (50 ppb annual average). Exceptionally high levels were found in one electric-stove home; subsequent evaluation indicated that the high levels were attributable to an unvented, gas-fired floor furnace. While the results in

Table 3. Characteristics of Eligible and Participating Households, First Pilot Study, Phase 1

Characteristic	Number	Eligible (% of total)	Participated (% of eligible)
Place of delivery			
University of NM	617	21.4	47.0
Lovelace	264	46.2	67.2
Type of screening			
Hospital	611	27.2[a]	51.8
Telephone	270	32.6	65.9
Maternal age (yr)			
14–17	54	—	—
18–20	189	26.5	36.0
21–25	289	28.7	57.8
26–30	177	42.9	64.5
31–35	73	45.2	69.7
⩾ 36	29	34.5	60.0
Ethnic group			
Anglo	239	46.9[a]	70.5
Hispanic	294	39.8	47.0
Other	60	41.0	40.0
Stove type			
Gas	346	40.5[a]	55.0[a]
Electric	247	46.1	58.8
Number in family			
2–3	185	44.9	54.2
4	211	49.8	67.6
5–7	197	33.5	42.4
Number of children			
1	224	39.7	52.8[a]
2	219	50.2	62.7
⩾ 3	150	36.7	50.9

[a] $p > 0.05$ for the association of this characteristic and eligibility or participation status. All other associations in the table were statistically significant at $p < 0.05$.

Table 2. Reasons for Ineligibility of Potential Subjects by Screening Approach, First Pilot Study, Phase 1

Characteristic	Screening Approach: Hospital (%)	Telephone (%)
Maternal age under 18 years	10.3	N/A
Infant in intensive care unit	7.6	N/A
Not fluent in English	6.7	1.1
Not available in hospital	7.1	N/A
No telephone[a]	17.8	6.6
Smokers in home	39.5	35.7
Day care	3.6	5.5
Other[b]	7.3	51.5

[a] The phone numbers of women who were screened by telephone were obtained from the hospital admitting office. In some cases, the phone had been disconnected or the phone number was not that of the woman herself.

[b] "Other" includes women who lived out of town or were moving. For telephone screenees, this category also included women whose listed phone numbers were wrong, who refused initial screening, or with whom contact was never established.

Table 4. Household and Demographic Characteristics by Stove Type, First Pilot Study, Phase 1

Characteristic	Gas Stove (%) (n = 100)	Electric Stove (%) (n = 44)
Type of housing[a]		
Single-family home	61.0	67.7
Duplex or apartment building	28.0	32.3
Mobile home	11.0	0.0
More than one bathroom[a]	32.9	60.0
House built 1979–1984	18.3	24.6
Walls insulated	53.7	50.8
Fireplace[a]	23.2	58.5
Primary heating source[a]		
Central forced-air furnace	59.3	83.1
Wall or floor furnace	33.3	15.4
Wood stove	8.5	6.2
Microwave oven[a]	25.6	51.5
Clothes dryer[a]	56.1	72.3
Household income[a]		
< $9,999	29.3	9.2
$10,000-$19,999	25.6	30.8
$20,000-$29,999	20.7	27.7
$30,000-$39,999	9.8	13.9
⩾ $40,000	4.9	9.2
No answer	9.8	9.2
Times per week stove is used for cooking		
Breakfast	4.6	3.8
Lunch	2.9	2.7
Dinner	6.1	5.9
Snacks	3.9	2.9
Family size		
Number of adults	2.1	2.1
Number of children	2.0	1.9
Parental education		
Father's years of education[a]	14.1	15.1
Mother's years of education	13.7	14.1

[a] $p < 0.05$.

this home were valid, they have been omitted in subsequent analyses.

Correlations of outdoor levels with indoor levels were somewhat higher in the electric-stove homes than in the gas-stove homes, and higher than expected in the gas-stove homes (Table 6). Within the two-week sampling cycles, correlations between activity-room and bedroom concentrations approached 0.9 in the gas-stove homes. In comparisons of the cycles, correlations were also high for the same rooms. The corresponding correlation coefficients were much lower in the electric-stove homes.

We used multiple regression analysis to assess the determinants of the NO_2 concentrations in the gas-stove homes and electric-stove homes. In the linear regression model, the significant determinants of NO_2 concentration were the outdoor concentration, the use of a gas stove, the presence of pilot lights on the stove, and, inversely, the use of a toaster or microwave oven in a home with a gas stove (Table 7). Other variables also affected the NO_2 level, although their effects did not attain the conventional level of statistical significance.

Phase 2

Particle Sampling. Indoor samples of respirable-size particles, less than 2.5-µm in aerodynamic diameter, were collected in each of the 49 homes using the impactor developed for indoor use. The samplers were located in the activity room of the house and operated continuously for one week (168 hours).

The one-week average concentrations of particles for 26 homes in the higher-NO_2 quartile group ranged from 8 to 82 $\mu g/m^3$ (Table 8). The average in the higher stratum of NO_2 was 28.3 $\mu g/m^3$, whereas the average in the lower stratum was 26.6 $\mu g/m^3$. By t test, the one-week mean concentrations were not significantly different between the two groups, and the one-week respirable-particle and NO_2 concentrations were not correlated.

The outdoor concentrations of particles varied by dates of sampling and location. Most ranged from approximately 10 to 30 $\mu g/m^3$, but a high value of 79.8 $\mu g/m^3$ was recorded at location 3, a city-maintained station located streetside at a major intersection. The elemental analysis showed generally comparable mean levels in the indoor and outdoor samples (Figure 6). Levels of silicon, calcium, and chlorine were much higher in the indoor samples, however.

Formaldehyde. Week-long formaldehyde (HCHO) concentrations were measured using the Air Quality Research, Inc., passive formaldehyde diffusion tube. Because sufficient samplers were not available, only 11 homes were tested: 4 homes from the upper and 7 from the lower stratum of NO_2 concentration. All integrated samples were less than 0.1 ppm, and the overall mean was 0.05 ppm. While these few measurements do not provide an adequate test of differences between the NO_2 exposure groups, the concentrations are typical of those in homes without substantial formaldehyde sources.

Water Vapor. Week-long water-vapor measurements were taken in all homes, using a diffusion sampling tube modified from the Lawrence Berkeley Laboratory design (Girman et al. 1984). The overall mean relative humidity was 35.89 percent (± 12.09 percent SD), and the values were

Table 5. Means, Medians, and Percentiles of Two-Week Nitrogen Dioxide Levels[a] in Homes Studied by Stove Type, First Pilot Study, Phase 1

		First Two-Week Sampling Cycle		Second Two-Week Sampling Cycle	
Location of Sampler	Statistic	Gas Stove	Electric Stove	Gas Stove	Electric Stove
Outdoors	Mean	19.1	14.2	20.3	19.6
	SD	4.8	5.7	5.5	7.4
	75th percentile	22.8	18.6	24.9	25.4
	Median	19.7	14.3	19.4	21.8
	25th percentile	15.9	10.4	16.2	11.9
Activity room	Mean	41.3	7.8	39.3	7.0
	SD	24.2	4.3	23.6	5.3
	75th percentile	55.3	10.5	45.3	8.7
	Median	35.5	6.9	35.1	5.6
	25th percentile	23.3	4.3	22.8	3.4
Bedroom	Mean	33.1	7.0	30.9	6.2
	SD	24.8	5.3	23.9	4.3
	75th percentile	41.9	8.7	36.3	7.6
	Median	26.6	5.6	24.6	5.0
	25th percentile	16.5	3.4	14.8	3.2

[a] All values are given in ppb.

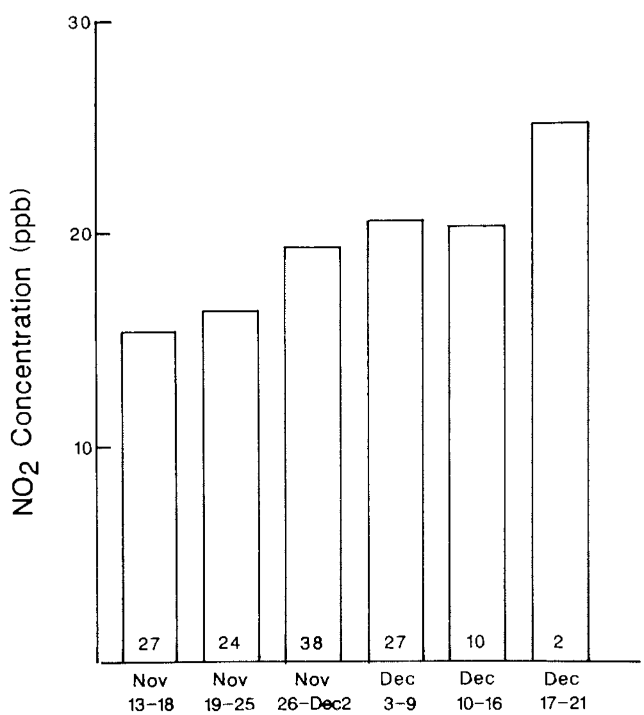

Figure 1. NO_2 mean concentrations (ppb) outdoors by date that sampling was started, First Pilot Study, Phase 1. The number of measurements is given within each bar.

comparable in the homes with low-NO_2 concentrations and those with high-NO_2 concentrations.

Air-Exchange Rates. Air-exchange rates were measured using a perfluorocarbon tracer system with one set of sources placed in the kitchen and another set of sources of a second tracer placed throughout the home. The mean air exchange, based on the average of the measurements, was 0.32 (± 0.3 SD) per hour. The median value was approximately 0.5 per hour. Most values were below 1.0 air exchange per hour (Figure 7).

One-Week Nitrogen Dioxide Concentrations. Each home was sampled for a one-week period between January and March 1985, according to the protocol described in the Methods section. As would be anticipated from the approach used to select the homes, NO_2 concentrations differed dramatically between the gas-stove (higher-NO_2) group and the electric-stove (lower-NO_2) group (Table 9). In the gas-stove homes, concentrations were similar in the kitchen and activity room, but were lower in the infant's bedroom. Outdoor concentrations were generally low. The median outdoor concentration was 12.8 ppb, but 5 of the 47 one-week measurements were above 20 ppb. At some sites, the outdoor concentrations were well above those observed in electric-stove homes.

In eight gas-stove homes and two electric-stove homes,

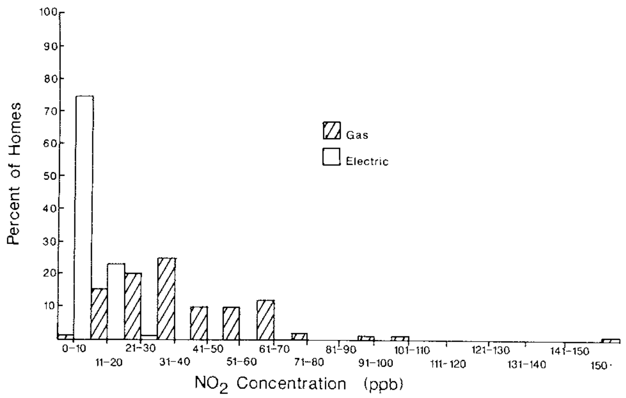

Figure 2. NO_2 mean concentrations (ppb) in the activity rooms. First measurement cycle, First Pilot Study, Phase 1.

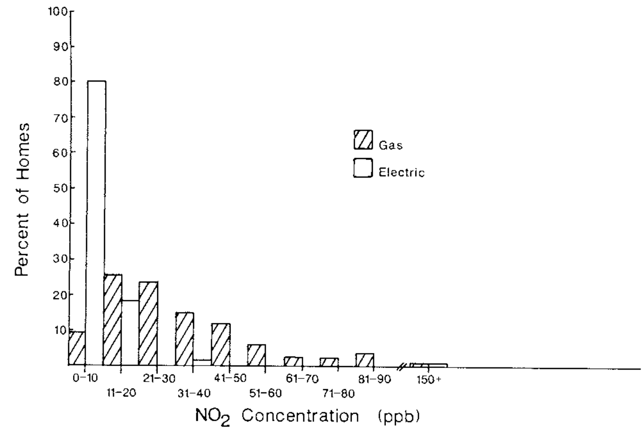

Figure 4. NO_2 mean concentrations (ppb) in the infants' bedrooms. First measurement cycle, First Pilot Study, Phase 1.

strings of Palmes tubes were hung in the activity room to monitor vertical gradients of NO_2. From floor to ceiling, we observed an increasing gradient of about 10 ppb.

Serial One-Day Nitrogen Dioxide Concentrations. To characterize day-to-day variation of NO_2 concentration, eight households were enrolled in a special study that involved seven serial one-day measurements. Filter badges were placed in the activity room and changed daily. The results (Figure 8) showed substantial variation in daily NO_2 levels, although three homes tended to have lower concentrations and one had consistently higher concentrations.

One-Day Nitrogen Dioxide Concentrations. During the week that the homes were monitored for NO_2, a field technician visited each home from the upper quartile of NO_2 concentration and made a series of shorter-term measurements of NO_2. One-day samples were obtained with filter badges placed in the kitchen, in the infant's bedroom, and on the infant's clothing or immediately adjacent to the infant. The sampling generally began in the morning, and parents were asked to place the badges in sealed jars at bedtime. One additional sample resulted from combining a prototype cartridge from General Motors with a low-flow air pump that was placed in the kitchen; the pump operated during any cooking to provide a measure of peak levels.

The highest levels were measured with the pump sampler in the kitchen during cooking (Table 10). The peak was 263 ppb and the median of the 14 values was 105 ppb. However, sampler tubes placed on the ceiling directly over the range had recorded a lower mean NO_2 level, at 56.7 ppb, which reflects longer averaging times. The one-day NO_2 concentrations measured by samplers located in the kitchen, but away from the direct influence of the range, were lower, and the one-week concentrations were still lower, as

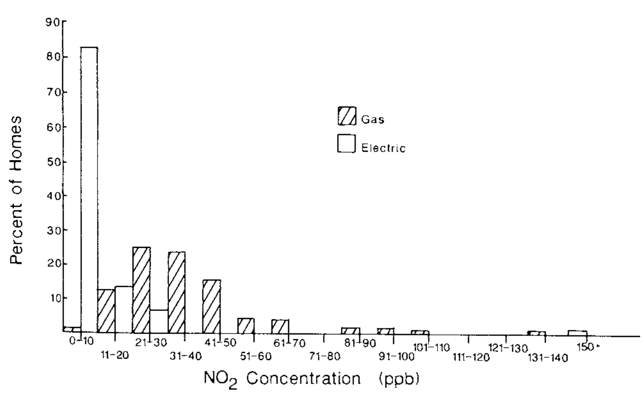

Figure 3. NO_2 mean concentrations (ppb) in the activity rooms. Second measurement cycle, First Pilot Study, Phase 1.

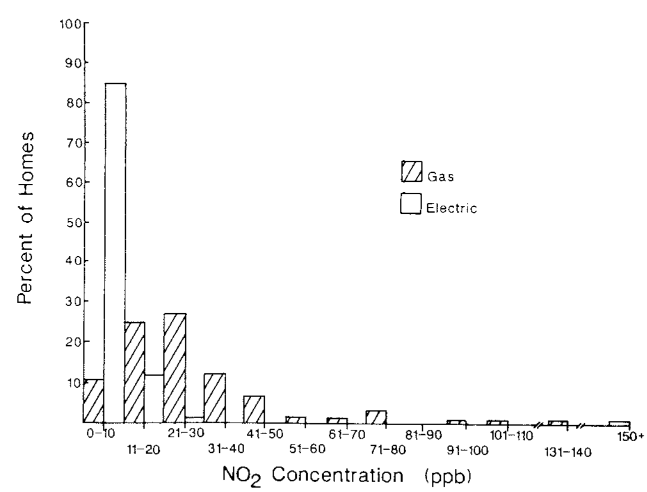

Figure 5. NO_2 mean concentrations (ppb) in the infants' bedrooms. Second measurement cycle, First Pilot Study, Phase 1.

Table 6. Correlations Between Two-Week Mean Nitrogen Dioxide Levels at Various Locations and During Sampling Cycles 1 and 2, First Pilot Study, Phase 1

Location/Cycle	Activity Room/1	Activity Room/2	Bedroom/1	Bedroom/2
Total Population				
Outdoors/1	0.52	0.45	0.47	0.44
Outdoors/2	0.35	0.38	0.43	0.42
Activity room/1		0.87	0.93	0.85
Activity room/2			0.83	0.92
Bedroom/1				0.91
Gas-Stove Homes				
Outdoors/1	0.44	0.30[a]	0.40	0.31[a]
Outdoors/2	0.54	0.49	0.62	0.60
Activity room/1		0.77	0.90	0.78
Activity room/2			0.75	0.88
Bedroom/1				0.88
Electric-Stove Homes				
Outdoors/1	0.46	0.51	0.50	0.60
Outdoors/2	0.47	0.64	0.48	0.57
Activity room/1		0.70	0.76	0.64
Activity room/2			0.47	0.76
Bedroom/1				0.56

[a] $p > 0.05$. All other correlation coefficients are statistically significant.

would be anticipated (Table 11). The pattern of variation of NO_2 concentrations—kitchen highest, activity room intermediate, and bedroom lowest—was similar for the one-day and one-week concentrations.

Table 7. Results of Multiple Regression Analysis for Predicting Nitrogen Dioxide Levels in the Activity Room, First Pilot Study, Phase 1

Variable[a]	Regression Coefficient	95 Percent Confidence Interval
Outdoor concentration	0.6	0.12, 1.0
Gas stove without pilot light	16.2	8.3, 24.1
Gas stove with pilot light	33.7	28.0, 39.4
Gas dryer in living space	5.1	− 1.1, 11.3
Floor or wall furnace	4.9	− 0.3, 10.2
Use of toaster oven or microwave or both in gas-stove homes	− 9.9	− 16.0, − 3.7
Income[b]	− 2.0	− 4.1, 0.1
Intercept	2.5	
$R^2 = 0.69$		

[a] All variables, with the exceptions of outdoor concentration and income, were dichotomous (1 = present, 0 = absent).

[b] Income defined as: 1 = ≤ \$9,999; 2 = \$10,000 to \$19,999; 3 = \$20,000 to \$29,999; 4 = \$30,000 to \$39,999; 5 = ≥ \$40,000.

Time-Activity Patterns of Infants. Time-activity logs were completed for each infant included in Phase 2. Not surprisingly, we found that the infants spent the greatest proportion of the day in the bedroom (Figure 9). However, during

Table 8. Stem and Leaf Diagram of Particle Concentrations ($\mu g/m^3$, Particulate Matter < 2.5 μm in Diameter) by Nitrogen Dioxide Strata, First Pilot Study, Phase 2

	Higher-NO_2 Homes		Lower-NO_2 Homes
		90	
	2	80	
	7 7	70	7
		60	
		50	6
	7 6	40	3 4 5 5
	7 5 0	30	2 3
	9 7 3 2 1 1 0	20	1 1 6 6
	9 9 9 9 4 4 1	10	0 1 2 4 4 6 6 8 8
	9 8 8	00	4 6
Number	25		23
Mean	28.3		26.6
SD	25		18.1
Median	25		23.5

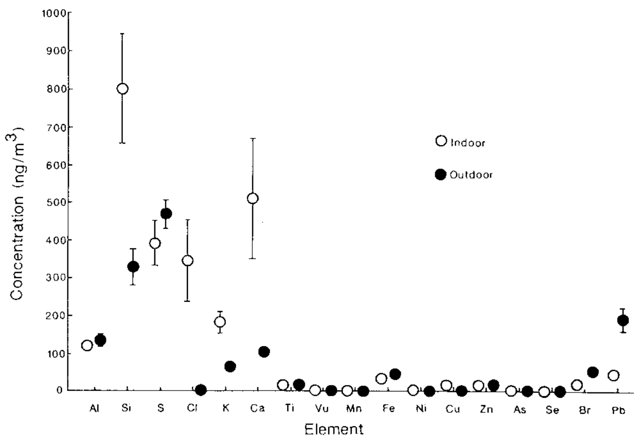

Figure 6. Means of elemental concentrations in indoor and outdoor particulate samples, First Pilot Study, Phase 2.

Table 9. One-Week Average Nitrogen Dioxide Concentration in Homes in the Upper- and Lower-Nitrogen-Dioxide Strata, First Pilot Study, Phase 2

	Higher-NO_2 Homes[a]	Lower-NO_2 Homes[a]
Kitchen	37.0 ± 21.0	3.5 ± 2.8
Activity room	35.0 ± 16.0	2.7 ± 2.9
Infant's bedroom	22.0 ± 14.0	2.9 ± 3.1
Outdoors	12.4 ± 8.8	8.2 ± 6.5

[a] Values are means ± SD in ppb.

the day, as much time was spent in the activity room as in the bedroom. Kitchen visits were short on average, but tended to take place during afternoon and evening hours, when NO_2 levels were more likely to be elevated by cooking. Travel occurred largely during the midday hours and early evening.

Estimated Personal Exposure to Nitrogen Dioxide. Estimates of personal exposure to NO_2 were constructed for each infant from the time-activity records and the NO_2 levels for the corresponding locations by summing the products of the NO_2 concentration and the time spent in each microenvironment. The time-weighted estimate of personal NO_2 (PNO_2) exposure for the *i*th individual is:

$$(PNO_2)_i = \{W_{ij} \times (NO_2)_{ij}\}$$

where $(PNO_2)_i$ is the integrated exposure of the *i*th individual for *j*th microenvironment; W_{ij} is the fractional time in the *j*th microenvironment for the *i*th individual; and $(NO_2)_{ij}$ is the average NO_2 concentration in the *j*th microenvironment for the *i*th individual. Both the one-week and the one-day NO_2 concentrations were used to construct separate estimates of personal exposure to NO_2.

Using the samples taken on the day of intensive monitoring, we estimated the average contribution of each microenvironment to personal exposure (Table 12). The dominance of bedroom concentrations is evident, but exposure in the activity room contributed 31.6 percent of total exposure on average.

Personal exposure, as measured on the day of intensive monitoring, was strongly correlated with the predicted per-

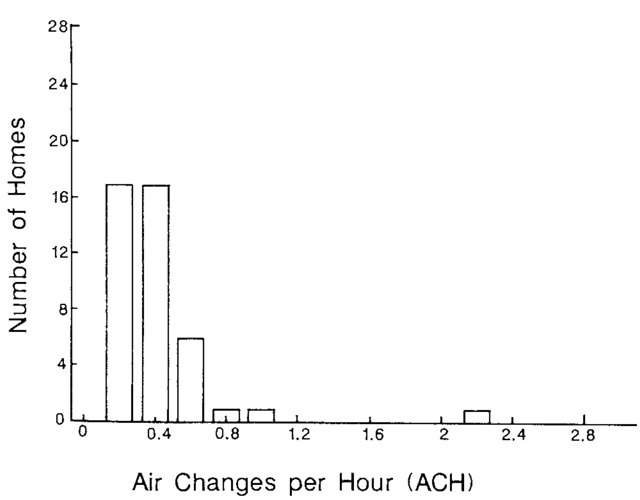

Figure 7. One-week average home air-exchange rates, First Pilot Study, Phase 2.

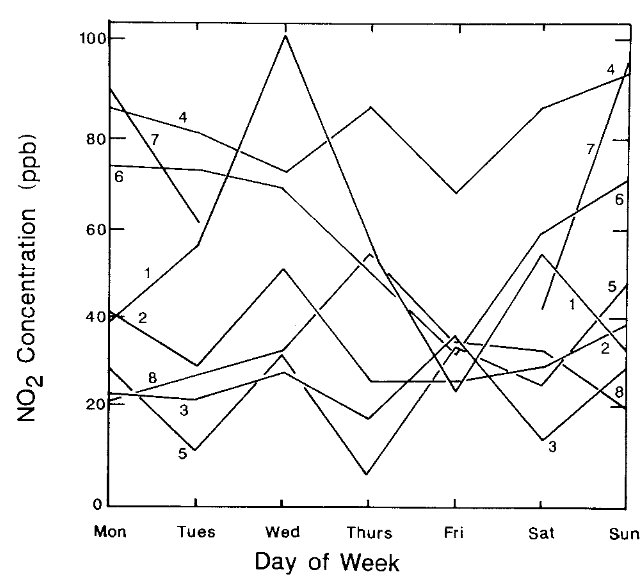

Figure 8. Successive daily 12-hour NO_2 levels in living rooms of eight homes, First Pilot Study, Phase 2. (Reproduced with permission from Harlos et al. 1987 and from Pergamon Press.)

Table 10. Stem and Leaf Display of Nitrogen Dioxide Concentrations (ppb × 10) in the Kitchens of Gas-Stove Homes, First Pilot Study, Phase 2

	Pump Sampler During Cooking Period		Ceiling Tubes	Day		Week
	High (263)	.				
		.				
		.				
	1 0	16		0	16	
		15			15	
	4	14			14	
	4	13			13	
		12			12	
	8	11			11	
	9 1	10	0	6	10	
		9	2 8 9	8 1	9	
	2	8	5		8	1
	8	7	4 8 9	0	7	3
	1 1 0	6		9 7 6 6 1	6	
		5	0 2 4 5 7 8	6 4	5	4 7 9
		4		9 6 1	4	1 3 5 6
	8	3	7	7 6 4 0	3	3 9
		2	0		2	5 6
		1	2 8		1	0 1 3 7 9
		0	8 8		0	8
Number	14		20	19		19
Mean	112.1		56.7	65.1		36.8
SD	58.6		31.4	31.39		21.6
Median	105		56	55		36

Table 11. Stem and Leaf Display of Nitrogen Dioxide Concentrations (ppb × 10) in the Kitchen, Activity Room, and Bedroom, and of Measured Personal Exposure of Gas-Stove Homes, First Pilot Study, Phase 2

	Kitchen			Activity Room			Bedroom			Personal	
	Day		Week	Day		Week	Day		Week	Day	
	High (160)	.								High (114)	.
		.									.
		.									.
	6	10			10			10			10
	8 1	9			9			9			9
		8	1	7	8			8			8
	0	7	3	3	7		2 0	7			7
	9 7 6 6 1	6			6	0	5	6		6	6
	6 4	5	4 7 9	6	5	1 4 6	9 1 0	5	0	7 0	5
	9 6 1	4	1 3 5 6		4	0 6	6 6 5 4 1	4	2	9 6 6 1	4
	7 6 4 0	3	3 9	4 4	3	9	4 2 1 0	3	1 1 2	7 5 4 3 0	3
		2	5 6	9 8	2	1 2 4 6 7	7 5 4 4	2	0 1 3 6	9 8 6	2
		1	0 1 3 7 9		1	0 8		1	0 1 4 5		1
		0	8		0			0	9		0
Number	19		19	7		14	19		14	15	
Mean	65.1		36.8	48.7		35.2	42.9		23.9	40.5	
SD	31.4		21.6	23.7		16.1	15.4		12.3	11.6	
Median	55		36	34		33	43		22	36	

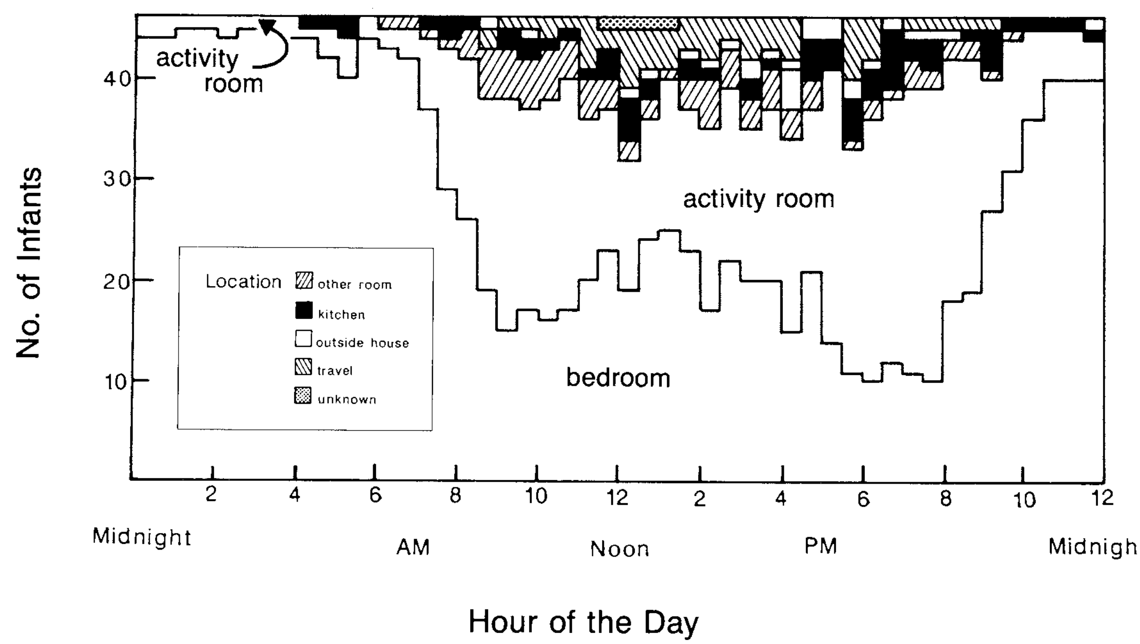

Figure 9. Time-Location Profiles for 46 Infants, First Pilot Study, Phase 2. (Reproduced with permission from Harlos et al. 1987 and from Pergamon Press.)

sonal NO_2 exposure (Table 13). It was also strongly correlated with the bedroom concentration on the same day. More modest correlations between personal exposure and kitchen measurements on the day of intensive monitoring were observed. Correlation coefficients for the hourly measurements in the kitchen with the day-long and week-long measurements in the kitchen were low.

We developed a series of regression models to predict personal NO_2 exposure (Table 14). In these models, the dependent variable was the NO_2 concentration measured by the filter badge that was placed on the infant's clothing for the active portion of the day. We assumed that these measurements were the true personal NO_2 exposures. This assumption may have been violated by unintentional shielding of the badge-face or by failure to keep the badges with the infants. The independent variables were various combinations of bedroom NO_2, kitchen NO_2, and hours of stove use.

Initially, we assessed the week-long measurements as predictors of measured day-long exposure. However, neither the bedroom NO_2 concentration measured for a week nor a personal-exposure estimate based on the week-long measurements predicted the actual daily exposure. Because NO_2 levels varied widely on a daily basis (Figure 8), we could not predict exposure on a particular day with measurements averaged over a week. In contrast, the measured exposures were strongly predicted in models (I, III, IV, V) that included the bedroom NO_2 concentration on the day that personal exposure was measured (Table 14). The R-squared value was lowest for the model (II) that included only kitchen NO_2 concentration. Examination of residuals from these regressions indicates that the models tended to overpredict personal exposure in homes with higher week-long bedroom NO_2 levels and to underpredict for lower week-long bedroom NO_2 levels.

Table 12. Average Contribution of Various Microenvironments to Estimated 24-Hour Nitrogen Dioxide Exposures of Infants, First Pilot Study, Phase 2

Location	Time × (hours ± SD)	Average NO_2 = (ppb)	Exposure (ppb × hr)	Portion (% total)
Bedroom	14.1 ± 6.2	57	804	63.0
Activity room	6.3 ± 4.5	64	403	31.6
Kitchen	0.8 ± 0.7	72	58	4.5
Outdoors	0.2 ± 0.3	11	2.2	0.2
Travel	0.9 ± 1.0	11	9.9	0.8
Total	24.0	–	1,277	100.1

Phase 3

In this phase, we tested the proposed surveillance methodology for respiratory illnesses, including the calendar-diary, the periodic telephone calls, and the assessment of

Table 13. Matrix of Pearson Correlation Coefficients Among Measured Exposure, Estimated Exposure, Stove Use, and Room Concentrations for Infants in Higher-Nitrogen-Dioxide Homes, First Pilot Study, Phase 2

		Actual Measurements				
Estimates	PNO_2[a]	Bedroom (day)	Stove Use (hour)	Kitchen (peak)	Kitchen (day)	Kitchen (week)
PNO_2[b]	0.83					
Bedroom (day)	0.78					
Stove use (hour)	0.53	0.49				
Kitchen (peak)	0.65	0.69	−0.18			
Kitchen (day)	0.70	0.68	0.32	0.36		
Kitchen (week)	0.43	0.27	−0.28	0.61	0.79	
Kitchen ceiling (week)	0.59	−0.07	−0.22	0.60	−0.04	0.77

[a] As measured by the Yanagisawa filter badge placed on the infant.
[b] Estimated from time-activity data and measurements.

Table 14. Least-Squares Regression Models for Predicting Personal Nitrogen Dioxide Exposures (ppb) of Infants in Higher-Nitrogen-Dioxide Homes, First Pilot Study, Phase 2

		Coefficents[a] for Variables in the Models			
Model	Intercept	Bedroom NO_2 (ppb)	Stove Use (hours)	Kitchen NO_2 (ppb)	R^2
I	13.2	0.7	—[b]	—	0.57
II	16.1	—	—	0.4	0.44
III	9.0[c]	0.5	—	0.22[c]	0.61
IV	7.1	0.8	—	—	0.70
V	5.2	0.7	2.1	—	0.71

[a] All coefficients refer to ppb.
[b] Variable not included in the model.
[c] $p > 0.05$. All other intercepts and coefficients significant at $p < 0.05$.

Table 15. Definition of Symptom Complexes for Respiratory Illness, First Pilot Study, Phase 3

	Symptoms[a]				
Symptom Complex	Wheezing	Cough	Nasal Congestion		Hoarseness
Lower respiratory infection	+	±	±		±
Cough alone	−	+	−		−
Upper respiratory infection with cough	−	+	+	or	+
Upper respiratory infection without cough	−	−	+		±
Hoarseness	−	−	−		+

[a] + = Symptom must be present; − = symptom must be absent; ± = symptom may be present, but not necessary.

Table 16. Number of Respiratory Illnesses[a] by Method of Ascertainment, First Pilot Study, Phase 3

	Calendar-Diary	Telephone
Lower respiratory infection	8	5
Cough alone	6	9
Upper respiratory infection with cough	42	32
Upper respiratory infection without cough	63	57
Hoarseness	1	2

[a] For definitions, see Table 15.

Table 17. Maternal Report of Infant Health Status by Nurse Practitioner Assessment, First Pilot Study, Phase 3

	Health Status Reported by Mother	
Nurse Practitioner Assessment	Sick	Well
Well	2	40
Nonrespiratory infection	1	1
Upper respiratory infection	46	3
Otitis media	8	0
Lower respiratory infection	4	0

ill children by a nurse practitioner. For Phase 3, 53 infants were selected. During the three-month surveillance period, only two infants were lost to follow-up: one whose family moved and one whose mother could not be regularly contacted. On average, each household received 5.8 calls, with a range of 4 to 8. Calendar-diaries were retrieved from all but two of the households. With few exceptions, the calendar-diaries appeared to have been filled out correctly. For example, mothers routinely entered the code "0" for days on which their child was asymptomatic, rather than leaving the space blank.

We devised symptom-based definitions for the various respiratory illnesses identified by calendar or telephone surveillance (Table 15). The algorithms were largely based on those used in the Tecumseh study (Monto and Cavalaro 1971). In the infant, few symptoms are pathognomonic of lower respiratory illness. Cough may be present with upper or lower respiratory tract infections; infants cannot report chest pain; and they generally do not expectorate phlegm. Accordingly, we classified only those illnesses with wheezing as lower respiratory tract infections. Those with cough alone were maintained in a separate category.

The numbers of events obtained by the calendars and surveillance calls were similar (Table 16). Somewhat fewer illness episodes were picked up by the telephone calls, but the distributions of illness types were similar with the two methods. As would be anticipated, most illnesses were upper respiratory tract, with or without cough.

The nurse practitioner made 61 visits at times when chil-

Table 18. Nurse Practitioner Assessment of Signs and Symptoms at Time of Visit, First Pilot Study, Phase 3

	Nurse Practitioner's Diagnosis				
Assessment	Well	Nonrespiratory Illness	Upper Respiratory Illness	Otitis Media	Lower Respiratory Illness
Clinical History					
Rhinorrhea or nasal congestion	2	0	40	4	3
Cough	1	0	12	4	3
Wheezing	0	0	0	0	1
Hoarseness	1	0	2	0	0
Noisy breathing	0	0	7	1	3
Physical Findings					
Clear nasal discharge	5	1	37	5	4
Yellow-green nasal discharge	5	0	9	1	0
Wheeze	1	0	0	0	3
Rales	0	0	0	0	3
Rhonchi	0	0	4	0	4
Erythematous pharynx	3	0	15	5	2
Tympanic membrane inflamed	0	1	2	8	1
Number of Visits	44	2	49	8	4

dren were reported as ill, and 46 control visits when children had not been reported to be ill (Table 17). In only two cases did the nurse practitioner find no evidence of illness for a reportedly ill child; similarly, at the time of a control visit, children were infrequently ill. The nurse practitioner did not diagnose a lower respiratory illness on any of the control visits.

As would be anticipated, patterns of symptoms and signs differed by illness status at the time of evaluation by the nurse practitioner (Table 18). The nurse practitioner's diagnoses were made using a conventional clinical approach and were not based on standardized criteria.

We cross-tabulated the nurse practitioner's diagnoses with the illness status as determined by calendar-diary at the same time (Table 19). A small proportion of children classified as "well" by the calendar-diary had upper respiratory infections diagnosed by the nurse practitioner. All children considered to have lower respiratory illness by calendar-diary report were also diagnosed with respiratory infection by the nurse practitioner; however, the diagnoses from the two sources were not concordant for all episodes. In the two instances in which the nurse practitioner did not diagnose lower respiratory illness, the children had stopped wheezing at least two days before the visit.

Table 20 provides further details for the episodes of lower respiratory illness and illustrates the sensitivity of the calendar approach. Wheezing was reported by telephone or calendar for four of the five physician-diagnosed or nurse-practitioner-diagnosed episodes. In 7 of the 10 episodes of wheezing reported, the child was evaluated by a physician. The nurse practitioner's diagnoses were generally corroborated by the pediatricians'. Fluorescent antibody stains were not positive in any of these episodes.

SECOND PILOT STUDY

METHODS

The second pilot study was conducted with the primary purpose of refining the system for illness surveillance (Table 1). Additional goals were to test further the methods for exposure assessment and to evaluate recruitment of subjects through pediatric practices.

Recruitment

Subjects were recruited from the University of New Mexico Hospital, Lovelace Medical Center, and a large private pediatric practice in Albuquerque. Through these three sites, 75 households were recruited. Subject enrollment methods varied with each institution. Regardless of enrollment procedure, eligibility criteria included the following: the mother was 18 years of age or older, spoke English, lived in a household without smokers, did not plan to move out of town or put the infant in day care, and had delivered a baby of at least 2,500 g who did not need admission to a neonatal intensive care unit.

At the University of New Mexico Hospital, potential subjects were identified from the labor and delivery log. We abstracted the name and hospital number of each woman giving birth between July and December 1985, who was 18 years or older, received prenatal care locally, and gave birth to a baby weighing 2,500 g or more. The address and telephone number of each woman was obtained from the hospital admitting office. If no telephone number was listed, the woman was deleted from the list. A letter describing the study was sent to all remaining women. Within four to

Table 19. Symptom Complexes as Recorded on Calendar-Diary by Nurse Practitioner Assessment of Episode,[a] First Pilot Study, Phase 3

		Nurse Practitioner Assessment			
Calendar Symptom Complexes	Well	Nonrespiratory Infection	Upper Respiratory Infection	Upper Respiratory Infection with Otitis Media	Lower Respiratory Infection
Lower respiratory infection	0	0	1	1	2
Cough alone	0	0	0	1	0
Upper respiratory infection with cough	2	0	12	2	2
Upper respiratory infection without cough	1	0	23	2	0
Hoarseness	0	0	1	0	0
No symptoms	37	2	3	0	0

[a] This table represents all episodes for which there were both calendar information and a nurse practitioner visit.

Table 20. Symptoms Reported, Methods of Ascertainment, and Clinical Diagnoses of Infants with Potential Lower Respiratory Infection, First Pilot Study, Phase 3

	Wheezing Reported				Nurse Practitioner's Diagnosis			Physician's Diagnosis			
Child Number	Calendar	Phone	Home Visit	Cough Reported by Parent	Not Made	Lower Respiratory Infection	No Lower Respiratory Infection	Not Made	Lower Respiratory Infection	No Lower Respiratory Infection	Viral Culture
11015	X	X	X	X		X			X		X
11015	X	X	X	X		X			X		
11031	X	NM[a]	NM	X	X					X	
11044	X	NM		X			X	X			
20567		X		X		X			X		
21013	X		NM	X	X			X			
31011	X	X	NM	X	X				X		
31069	X		X	X			X			X	
31069				X		X		X			
61058	X		NM	X	X					X	

[a] NM = telephone call or home visit not made.

seven days of sending the letter, we called each potential subject to administer a screening questionnaire for determining eligibility. All eligible women were invited to participate until we reached a 7:3 ratio of gas stoves to electric stoves. Enrollment visits were arranged for the following week with those who accepted.

At Lovelace Medical Center, we employed recruitment methods similar to those used in the initial pilot study. Mothers on the postpartum floor were administered the same screening questionnaire. We explained the study to eligible women, gave them an information sheet, and told them that we would be calling within two to three weeks to ask if they were interested in participating in the study.

At the pediatric practice, the pediatricians were asked to give an information sheet about the study to each potential subject, and to tell her that we would call during the next week. The receptionist wrote down the name, child's age, and mother's telephone number for each child under six months who had been seen each day. The receptionist's log was picked up weekly. At the beginning of each telephone call, we asked the mother if the pediatrician had informed her about the study. Whether or not she had been told about the study, we described it quickly and then administered the screening questionnaire. If she was eligible, we explained the study in greater detail and invited participation. Appointments for the next week were scheduled with those who agreed.

Exposure Assessment

Three sampling strategies were employed in the second pilot study. Initial measurement visits were made to all homes (75) one to two weeks after the enrollment visit. During this visit, the field technician administered a detailed housing-characteristics questionnaire and placed Palmes tubes. Five tubes were placed in each home with a gas stove: one each in the activity room, kitchen, and outdoors, and two in the infant's bedroom. In homes with electric stoves, one tube was placed in the infant's bedroom and one outside. All indoor samples were between 2 and 6 ft above the floor. Outdoor samples were located on the north side of the home, away from windows, doors, or vents. All homes were visited at the end of two weeks to retrieve the tubes. This procedure was repeated six weeks later for 45 homes.

For a different group of 15 homes, the field technician explained proper tube placement to the respondents at the initial visit and requested that the respondents put up and take down a second and third set of two-week measurement tubes that would be mailed to them at six-week intervals. Participants who agreed were mailed tubes with preaddressed, stamped return mailers, instructions on recording times and dates, and instructions on opening, placing, recapping, and returning the tubes. Receipt and placement of the tubes were verified during routine surveillance calls.

The remaining 15 homes were monitored for six consecutive two-week periods. When the field technician retrieved the first set of tubes, she left five more sets and instructed the participants in placing the tubes and recording the times of uncapping and recapping. These tubes were returned by mail. Participants were reminded to change sets every two weeks during routine surveillance calls. In addition, the nurse practitioner checked on tube placement when she made a health assessment visit.

Surveillance

The design for the surveillance system was based on our experience with surveillance of 50 infants during the first pilot study. That experience showed that mothers would complete the calendar-diary and respond to telephone calls. We also documented that symptoms are quite nonspecific for infants and that clinicians' diagnoses had a variable relationship to reported symptoms. The second pilot study was undertaken to refine the surveillance system; we planned to assess (1) the utility of pulse oximetry for diagnosing the involvement of the lower respiratory tract, (2) the yield from an improved protocol for viral cultures, and (3) the necessity of making weekly, as compared with biweekly, telephone calls. An additional goal was to acquire data to describe further the relationships between parental reports of symptoms and illnesses and diagnoses by physician and nurse practitioner.

These objectives were met by follow-up of 75 infants during a three-month surveillance period, according to the protocol described below (Table 21). The nurse practitioner made an enrollment visit to each household; at this visit, which lasted about one hour, she explained the surveillance procedures, obtained a household census, administered the standard respiratory symptoms questionnaire developed by the American Thoracic Society (Ferris 1978) to each adult, and instructed the mother in the use of a rectal thermometer given to her to take her child's temperature. Additional base-line information was also obtained. A brief questionnaire was used to collect information on the baby's gestational age, breast-feeding, day care, and sources of medical care. The mother was also given postcards to be completed by the physician at the time of any visits for illness.

The surveillance procedures included a calendar-diary for symptoms that was filled out daily, and weekly or biweekly surveillance telephone calls. In the first pilot study, information was collected on cough without further specification. In the second pilot study, cough was classified as wet or dry. The mothers were also asked to telephone the office when the child became ill with respiratory symptoms. The 75 mothers were assigned randomly to be telephoned weekly or biweekly so that we could compare rates of symptom reporting.

If a parent-initiated or routine surveillance call indicated that an infant had respiratory symptoms that had developed within the past 72 hours, the nurse practitioner made arrangements for a home visit. These visits were timed to occur as close to 72 hours after symptom onset as possible. This interval was chosen after discussion with Dr. Caroline Hall, the project's consultant on respiratory illness surveillance. She suggested that 72 hours represented the best choice for obtaining positive viral cultures and for detecting lower respiratory tract manifestations of infection.

At this visit, the child was assessed by the nurse practitioner with a standardized clinical history and physical examination. The nurse practitioner's approach was standardized in advance of data collection by Dr. Alice Cushing, the project's pediatrician. Arterial oxygen saturation was measured with a pulse oximeter (Biox Model 3700, Ohmeda, Boulder, CO). The nurse practitioner obtained a nasal wash and throat swab for viral culture from every child she diagnosed with a lower respiratory illness and from every third child (later changed to every second child) with an upper respiratory illness. For every three ill children, the nurse practitioner randomly selected one control child who had not been reported as ill. The same clinical assessment protocol and virological work-up were performed on each control child.

Table 21. Methods of Respiratory Illness Surveillance, Second Pilot Study

Enrollment Visit Tasks	Parent Responsibilities	Acute-Illness Visits or Well-Child Checks
Parent's respiratory symptoms questionnaire	Maintain calendar-diary	Clinical history
Household census and base-line infant information	Respond to periodic surveillance calls	Standardized physical examination
Instruction in completion of calendar-diary	Call project office when child is sick	Pulse oximetry
Instruction in use of rectal thermometers	Give postcard to physician upon any visit for illness	Nasal wash and throat swab for every child with lower respiratory infection, every third child with upper respiratory infection, and all well children
Base-line pulse oximetry		
Postcards for pediatrician		
Informed consent		

RESULTS

Recruitment

We attempted to contact 669 women by telephone, 81 percent of whom had given birth at the University of New Mexico Hospital. The telephone number was either inaccurate or disconnected for 207 women (31 percent). Contact with the designated respondent was not achieved for 27 women (4 percent), and 10 women (1 percent) refused to answer the initial questionnaire. Of the 425 women who answered the questionnaire, 145 (34 percent) were eligible. However, 41 of these women were not asked to participate because their homes had an electric stove and the quota of households with electric stoves was already filled. Of the 104 women asked to participate, 75 (72 percent) agreed. These 75 did not include 4 women who originally agreed to participate but then were not successfully enrolled, and 2 women who were enrolled but soon returned to work and placed their children in full-time day care. Of the 75 women enrolled, 5 were lost to follow-up during the study period.

Characteristics of women who were eligible and who participated were similar to those of participants in the previous pilot study (Table 22; see also Table 3). Participation rates were highest among non-Hispanic whites, and increased with increasing maternal age and family size. Participation did not vary by stove type. Eligibility among women with electric stoves was artifactually low, since 41 women were ineligible only because they had electric stoves.

In-hospital recruitment from Lovelace Medical Center was less successful in this pilot study, in terms of both eligibility and participation rates, than in the previous pilot study. The reasons for the difference in recruitment between the two pilot studies were unclear. In contrast, recruitment from the pediatric practice was highly successful. Although the majority of women in this practice had not, in fact, heard about the study from their pediatricians, they were very receptive when told that their pediatricians were cooperating and had provided us with their names and telephone numbers. If we had not stratified the sample

Table 22. Characteristics of Eligible and Participating Respondents, Second Pilot Study

Characteristic	Total Number	Eligible (% of total)	Participating (% of eligible)
Place of ascertainment			
University of New Mexico Hospital	545	13.0	70.4
Lovelace Medical Center	40	22.5	33.3
Pediatric practice	81	28.4	91.3
Other	3	33.3	100.0
Maternal age			
17–20	167	13.2	54.5
21–25	253	13.4	70.6
26–30	143	21.7	77.4
31–35	65	21.5	85.7
36–43	26	11.5	100.0
Unknown	15	—	—
Ethnic group			
Anglo	174	25.3	88.6
Hispanic	182	29.7	57.4
Other	33	15.1	100.0
Unknown	280	—	—
Stove type			
Gas	216	33.3	72.7
Electric	181	17.7	71.9
Unknown	272	—	—
Number of children			
1	144	22.2	65.6
2	146	26.0	68.4
3–4	89	29.2	76.9
5–8	18	44.4	100.0
Unknown	272	—	—

by stove type, 42 of 81 women from this practice would have been eligible. Participation among the eligible women exceeded 90 percent.

The pace of recruitment was slower than anticipated. Enrollment visits took place between January 15 and March 7, 1986, although 75 percent of participants were enrolled by February 21. The length of the recruitment effort reflected the unexpectedly large number of initial information letters that were returned because the respondent had moved, and the large number of telephone numbers obtained from the admitting office of the University of New Mexico Hospital that were incorrect or not in service. We also had unanticipated problems in recruitment at Lovelace Medical Center, where we enrolled subjects only by face-to-face contact with women still on the postpartum ward. In addition, we were reluctant to contact eligible women until at least two weeks after they had given birth, a delay that further slowed the recruitment process.

Exposure Assessment

Examination of the housing characteristics by stove type demonstrated the same pattern of differences between households with gas stoves and those with electric stoves as in the first pilot study (Table 23; see also Table 4). The homes with electric stoves tended more often to be detached single family homes, to have more rooms, to be heated by a central forced-air furnace, and to have a fireplace and a microwave oven. A higher proportion of households with an electric stove had a mean annual income of $40,000 or more, and the parents of infants living in a home with an electric stove tended to have more education.

In measuring the NO_2 in this pilot study, we planned to test three sampling strategies and to obtain further documentation of residential NO_2 concentrations. With regard to the first objective, we assessed three approaches for measuring NO_2: samplers placed and retrieved by a technician, mailed samplers, and samplers placed by a respondent.

The overall success of NO_2 monitoring can be assessed by the number of target hours actually monitored and the number of valid samples. Overall, 92 percent of potential samples were obtained (Table 24). The difference between potential and actual return is largely due to attrition after the first round of monitoring: three respondents moved away, two withdrew from the study, and one person's house burned down. Tubes were not recovered from one person's house. The data were complete and valid for 85 percent of returned samples. Eight percent of homes had incomplete data: either a single tube's value was inconsistent with other household measurements or a tube was lost during sampling. The complete set of values for one round was voided in 7.3 percent of samples because the respondent forgot to write dates on the field card or because the values for a two-week period were inconsistent with other two-week measurements in the same home.

Table 23. Housing and Family Characteristics by Stove Type, Second Pilot Study

Characteristic	Gas Stove (%) (n = 56)	Electric Stove (%) (n = 24)
Type of building		
Single-family home	57.1	79.2
Duplex	8.9	4.2
Apartment building	21.4	12.5
Mobile home	12.5	4.2
Number of rooms		
1–3	12.5	8.3
4–5	55.3	41.7
⩾ 6	32.2	50.0
Primary source of heat		
Central warm-air furnace	60.7	83.3
Wall or floor furnace	25.0	8.3
Electric units	1.8	4.2
Wood stove	5.4	4.2
Other	7.2	0.0
Space heaters	5.4	0.0
Fireplace	26.8	58.3
Microwave oven	39.3	62.5
Number of adults		
1	5.4	0.0
2	75.0	83.3
3–5	19.7	16.7
Number of children		
1	23.2	37.5
2–3	58.9	54.1
⩾ 4	10.7	8.3
Father's education (yr)		
6–12	57.0	44.0
13–16	30.0	26.0
⩾ 17	13.0	30.0
Mother's education (yr)		
6–12	62.5	50.0
13–16	30.4	41.7
⩾ 17	7.1	8.3
Household income		
⩽ $9,999	21.4	20.8
$10,000-$19,999	35.7	20.8
$20,000-$29,999	25.0	12.5
$30,000-$39,999	10.7	16.7
⩾ $40,000	5.4	25.0
Unknown	1.8	4.2

As would be anticipated, technician-placed samplers yielded the highest rate of valid data capture: 95 percent,

Table 24. Sampling Results by Strategy for Tube Placement and Return, Second Pilot Study

Sampling Strategy	Stove Type	Potential Return (sets)	Actual Return (sets)	Complete	Partial[a]	Void[b]
Technician	Gas	62	58	54	4	0
	Electric	28	27	27	0	0
Mail	Gas	30	28	21	5	2
	Electric	15	15	12	3	0
Continuous	Gas	66	59	43	3	13
	Electric	24	19	18	1	0
Total	Gas	158	145	118	12	15
	Electric	67	61	57	4	0

[a] One tube was missing or the value was discarded because of inconsistency.

[b] Entire set of values for one round was discarded because of inconsistency with other measurements.

as compared to 77 percent for mailed samples and 78 percent for respondents sampled on a continuous basis. Only 7 of 15 houses assigned to continuous sampling had valid data for all six measurement intervals. Three people placed only four sets, one did not write dates on the field card for any set, one moved away, two people had one two-week set voided because of probable errors in date documentation, and the values for one household were completely inconsistent and uninterpretable. All the households that received tubes by mail had at least one set of valid data, in addition to the tubes placed by the technician. Only two sets of data had to be completely voided, and only one respondent failed to return the last set of tubes.

The second objective of the NO_2 exposure assessment was to provide further documentation of residential NO_2 levels in Albuquerque. The distribution of the two-week NO_2 concentrations demonstrates the same pattern that was observed during the previous year, although the indoor levels were lower than those measured in the first pilot study, probably due to the higher ambient temperatures during the second pilot study. In homes with electric stoves, ambient concentrations consistently exceeded indoor concentrations (Table 25). In homes with gas stoves, the NO_2 concentration was typically highest in the kitchen, followed by the activity room and the bedroom. Outdoor concentrations were lower. As noted in the previous study, the outdoor values for homes with electric stoves were slightly lower than for homes with gas stoves. This pattern most likely reflects the greater likelihood of homes with gas stoves being located in older parts of the city, where the higher density of mobile sources results in higher outdoor levels. The average outdoor and indoor NO_2 concentrations were both lower in the second round than in the first.

All indoor measurements were highly correlated, with Pearson correlation coefficients of 0.84 or above in homes with gas stoves (Table 26). Also in gas-stove homes, the correlations between indoor and outdoor measurements were low in both rounds. As would be expected, bedroom and outdoor concentrations were more highly correlated in homes with electric stoves: 0.80 during the first round and 0.74 during the second round. The correlations of measurements between rounds for the same room exceeded 0.92 in homes with gas stoves and 0.87 in homes with electric stoves (Table 26).

Eight homes were monitored during successive one-week periods to assess the potential error introduced by monitoring every six to eight weeks and interpolating between measurements to estimate exposure (Figure 10). Variability from measurement to measurement was greater in homes with high NO_2 concentrations.

Surveillance

Surveillance covered 75 infants for periods ranging from 51 to 137 days. First, we will consider the logistics of this system and compliance with the methods.

Implementation of the system required only one visit, lasting approximately one hour. All calendar-diaries were distributed at that visit and picked up at the end of the study. Of the 300 calendar-diaries given out, all but 30 were returned. On average, the field technicians made two attempts for each completed surveillance telephone call, with a range of 1.0 to 6.8 for individual subjects. Approximately 14 hours per week were devoted to making these calls by the field technicians.

Maternal compliance was assessed with three different indicators: comparisons of telephone and calendar reports of symptoms, numbers of parent-initiated calls, and num-

Table 25. Nitrogen Dioxide Concentrations[a] by Stove Type, Location, and Measurement Cycle, Second Pilot Study

Stove Type and Location of Tube	Mean	Percentiles 25%	50%	75%	Maximum NO_2 Measured
Electric Stove (n = 24)					
Bedroom					
Round 1	7.3	2.2	3.6	6.7	77.6
Round 2	3.6	1.7	2.6	4.3	9.6
Outdoors					
Round 1	8.8	4.9	7.7	12.0	19.2
Round 2	6.4	3.1	4.9	10.0	13.1
Gas Stove (n = 56)					
Kitchen					
Round 1	44.0	23.4	37.0	53.5	133.1
Round 2	36.2	21.1	31.0	42.9	117.3
Activity room					
Round 1	33.4	17.0	29.2	41.7	110.4
Round 2	28.0	13.8	21.4	37.4	92.0
Bedroom					
Round 1	30.4	13.6	21.2	31.5	77.9
Round 2	22.5	11.6	16.5	25.2	89.0
Outdoors					
Round 1	11.8	7.5	12.2	14.5	26.0
Round 2	9.5	5.8	9.6	12.0	24.3

[a] Concentrations given in ppb.

bers of postcards distributed to physicians at the time of visits for illness that were returned to our office. With regard to the comparison of telephone and calendar reports, we examined telephone information for the 61 calendar months for which parents recorded no symptoms at all. The telephone reports corroborated the absence of symptoms for 53 months, showed minor differences for 6 months, and provided conflicting information for 2 months. We also compared the detailed symptom reporting from telephone calls with every tenth calendar month (n = 26) and found perfect agreement for 17, close agreement for 7, and poor agreement for 2.

Table 26. Pearson Correlation Coefficients Between First and Second Measurement Cycles by Stove Type and Location, Second Pilot Study

Round 1	Round 2 Activity Room	Kitchen	Bed-room	Out-doors
Gas-Stove Homes				
Activity room	0.93	0.85	0.86	0.38[a]
Kitchen	0.84	0.95	0.88	0.32
Bedroom	0.89	0.91	0.93	0.44
Outdoors	0.58	0.43	0.44	0.78
Electric-Stove Homes				
Bedroom	—	—	0.88	0.61
Outdoors	—	—	0.82	0.87

[a] p = 0.02.

Of the 216 illness events identified by the surveillance

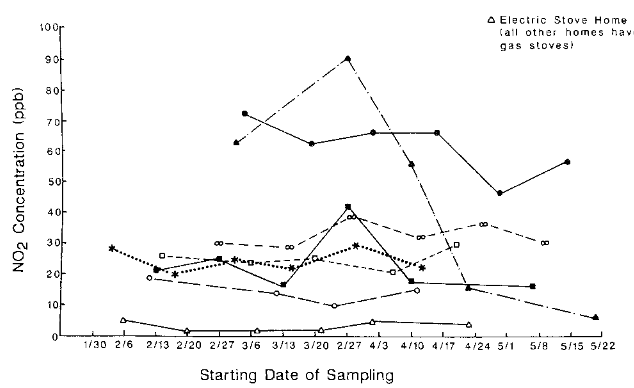

Figure 10. Results of successive one-week monitoring for NO_2 concentrations (ppb) in eight homes. Second Pilot Study.

system, 49 (23 percent) were through parent-initiated calls. The likelihood of a parent-initiated call was only weakly related to the type of syndrome or the presence of fever.

Reviewers of the initial proposal urged that surveillance calls be made weekly, rather than biweekly as originally planned. Because of the additional staff needed to make weekly calls, we undertook a comparison of weekly and biweekly calls. We were not aware of any previous systematic investigation of calling frequency, other than a study reported by Tager and Speizer (1976).

We assessed the effect of calling frequency by randomizing the infants to weekly or biweekly calling groups. The characteristics of the two groups were comparable. Weekly calls yielded higher rates of reporting for some symptoms, but for only one (wet cough) of the two symptoms (wet cough and wheeze) that we considered indicative of a lower respiratory tract process (Table 27). Similarly, upper respiratory infection and wet cough syndromes were reported more frequently in the weekly group. We did not find that parents in the weekly group were more likely to initiate calls when their children were ill.

Several approaches can be used to characterize the validity of the surveillance system. The results can be compared against other measures; for example, nurse practitioner or physician diagnosis, and viral culture. Within the limitation of sample size, the results can be examined descriptively for their plausibility and for the effects of factors known to influence illness rates. We anticipated higher rates in males and in families with more than one child, and an overall illness rate of six to eight episodes annually (Glezen and Denny 1973). A male excess was not present, although effects of family size on upper and lower respiratory tract syndromes were evident (Table 28). Reporting was not influenced by ethnicity, nor consistently by socioeconomic status. We have calculated annualized rates based on observation for approximately one-fourth of the year; while extrapolation to one year should be considered cautiously, the rates for upper and lower respiratory symptoms are comparable to those from other surveillance systems. For example, children under one year of age averaged 6.1 illnesses per year in Tecumseh, MI (Monto and Ullman 1974), and nearly 9 per year in the Houston Family Study (Gardner et al. 1984).

Table 27. Comparison of Symptoms and Illness Rates by Surveillance Call Frequency, Second Pilot Study

	Mean Number of Days with Symptom	
Symptom	Weekly Calls	Biweekly Calls
Noisy breathing	4.4	5.1
Hoarseness	0.9	1.3
Red eyes	2.7	1.1
Runny nose	20.3	17.5
Dry cough	5.7	5.8
Wet cough	5.1	3.8
Wheezing	0.8	1.5
Temperature	2.5	1.5
	Annualized Incidence of Illness Syndromes[a]	
	Weekly	Biweekly
Upper respiratory infection	8.0	5.4
Wet cough	2.2	0.9
Wheeze	1.2	1.2

[a] A syndrome was designated an upper respiratory infection if hoarseness, rhinitis, or dry cough was present, but not a wet cough or wheezing. A wet cough was defined as any constellation of syndromes that included a wet cough but did not include wheezing. Any group of symptoms that included wheezing was considered a wheeze syndrome.

Table 28. Incidence Rates for Three Syndromes by Demographic Characteristics, Second Pilot Study

	Calendar Syndromes[a]		
Characteristic	Upper Respiratory Infection	Wet Cough	Wheeze
Stove type			
Gas	7.46	1.58	1.36
Electric	5.25	1.56	0.85
Infant gender			
Male	7.48	1.33	0.92
Female	6.06	1.78	1.43
Ethnicity[b]			
Anglo	6.23	1.53	1.26
Hispanic	6.70	1.73	0.81
Number of children			
1	5.26	1.53	0.51
⩾ 2	7.29	1.59	1.46
Household population			
2–3	5.51	1.50	0.50
4	7.99	1.28	1.14
⩾ 5	6.63	1.88	1.75
Socioeconomic status[c]			
Low income, low education	7.68	1.36	1.51
High income, low education	6.69	0.33	0.33
Low income, high education	8.14	3.15	1.57
High income, high education	5.40	1.86	0.84

[a] For definitions see Table 27.

[b] Does not include Orientals and Blacks.

[c] Low income is defined as income below $20,000; low education is defined as less than 13 years of education.

Table 29. Comparison of Syndromes from Surveillance Calendar with Nurse Practitioner Diagnoses

	Nurse Diagnosis				
	Upper Respiratory Infection	Otitis Media	Lower Respiratory Infection	No Visit	Total
Calendar Syndromes Expanded					
Upper respiratory infection	24	5	0	89	118
Upper respiratory infection with fever	6	0	2	16	24
Wet cough	7	1	3	14	25
Wet cough with fever	4	1	1	2	8
Wheeze	5	1	3	8	17
Wheeze with fever	1	0	1	6	8
Total	47	8	10	135	200
Calendar Syndromes Reduced					
Upper respiratory infection	30	5	2	105	142
Wet cough	11	2	4	16	33
Wheeze	6	1	4	14	25
Total	47	8	10	135	200

We also compared the data from the surveillance system with the diagnoses made by the project's nurse practitioner and by physicians, if consulted. We did not find a tight correspondence between the nurse practitioner's diagnoses and calendar reporting by the parent (Table 29). However, of the 10 diagnosed lower respiratory illnesses, 8 were accompanied by a report of wet cough or wheeze through the surveillance system. For this reason, we reduced the six original syndrome categories to three: upper respiratory illness, any wet cough, and any wheeze.

For physician diagnoses, a similar pattern was observed (Table 30). A total of 13 lower respiratory illnesses were diagnosed by either a physician or the nurse practitioner. Of these, 11 were accompanied by wet cough or wheezing, a sensitivity of 85 percent for detecting lower respiratory illness with these symptoms. As would be anticipated, the specificity was lower, at 70 percent.

Comparison of the surveillance results to viral cultures is another approach for validation. Unfortunately, our surveillance period was subsequent to the annual epidemic of respiratory syncytial virus infection. The overall culture yield was 34 percent, and was 35 percent in ill children (Tables 31 and 32).

PROPOSED DATA ANALYSIS

Introduction

During the second pilot study, we also considered methods to analyze the data to be collected in the proposed cohort study. This section relates the evolution of the plans for analysis and the rationale for the proposed analytical strategy.

The original reports concerning NO_2 exposure from gas stoves and children's health were based on cross-sectional data; observations on health effects and type of cooking stove were made at a single point in time (see, for example, Melia et al. 1977 and Speizer et al. 1980). Most of the subse-

Table 30. Comparison of Calendar Syndromes with Physician Diagnoses, Second Pilot Study

	Physician Diagnosis						
Calendar Syndrome	Upper Respiratory Infection	Otitis Media	Lower Respiratory Infection	Other	No Visit	Unknown	Total
Upper respiratory infection	8	18	0	2	111	2	141
Wet cough	5	5	3	1	19	0	33
Wheeze	2	5	2	2	14	0	25
Total	15	28	5	5	144	2	198

Table 31. Viral Isolates, Second Pilot Study

Type of Isolate	Number
Rhinovirus	2
Parainfluenza 1	1
Parainfluenza 3	2
Adenovirus 1	2
Adenovirus 2	3
Influenza A	1
Poliovirus 1	1
Cytomegalovirus	4
Echovirus	1
Coxsackie B4	1
Trichomonas vaginalis	1

quent data have also been cross-sectional, although cohort and case-control studies have now been reported (see, for example, Jones et al. 1983 and Berkey et al. 1986). The cross-sectional design provides an assessment of the effects of cumulative exposure; inherently, the temporal profile of exposure is lost with this design. In the longitudinal studies, the exposure variables have also represented only cumulative exposure to NO_2.

For respiratory illnesses in infants, presumably of infectious etiology, cumulative exposure to NO_2 seems less relevant than an exposure classification system that temporally varies. In vitro models of effects on immune function show rapid responses (Morrow 1984), and the animal infection models have generally involved acute exposures to NO_2 (Jakab 1980; Morrow 1984). Accordingly, for the cohort study, we developed a plan to temporally characterize exposure to the extent possible with the measurements that can feasibly be made in an epidemiological study. The approach to analysis should also permit the type of cumulative exposure assessment performed by others.

We plan to use the periodic two-week NO_2 measurements to establish the temporal profile of exposure during the entire period of observation. We propose to use interpolation and extrapolation to assign an NO_2 value to each day of observation. This procedure requires the assumption that two-week averaged NO_2 concentrations vary smoothly, an assumption supported by the gentle trends of meteorological change with the seasons (averaged over several weeks).

Thus, the cohort study will be designed as an incidence density study rather than a cumulative incidence study, and illness will be related to the exposure sustained before it developed, rather than cumulating all illnesses and relating the total to cumulative exposure. The cohort study will also be analyzed as a cumulative study to replicate the efforts of others.

Analysis Based on Cumulative Exposure

Even though the cumulative exposure approach seems less satisfactory than an approach that permits exposure to vary temporally, we will analyze the cumulative illness experience of each child in relation to cumulative exposure using stratified methods and logistic modeling.

The primary outcome measures will be the incidence rates of the various syndromes, across the entire observation period for each child: the cumulative incidence of physician-diagnosed illnesses, the duration of illness episodes, and the number of days with the various symptoms. These measures will be examined in relationship to stove type and to cumulative exposure to NO_2. The principal measure of exposure will be the time-activity-weighted personal index for each infant across the entire observation period. We will also use a dichotomous variable for stove type. Misclassification from use of stove type as an exposure variable will be assessed.

Table 32. Viral Isolates by Nurse Practitioner Diagnosis, Second Pilot Study

	Nurse Practioner Diagnosis				
Viral Isolate	Well	Upper Respiratory Infection with Otitis Media	Bronchiolitis[a]	Unspecified Lower Respiratory Infection	Total
No wash	1	33	0	0	34
No isolate	15	15	3	4	37
Parainfluenza	0	2	1	0	3
Adenovirus	3	2	0	0	5
Rhinovirus	0	2	0	0	2
Influenza	0	1	0	0	1
Cytomegalovirus	3	0	1	0	4
Other	1	3	0	0	4

[a] Bronchiolitis is one form of lower respiratory infection.

With the cohort design, incidence rates of illness can be calculated directly and compared across strata of cumulative NO_2 exposure and of the various confounding factors (for example, see Table 33). For these incidence rates, the numerators will be the numbers of events within specific illness categories and the denominators will be the infant-months of follow-up time. The cumulative incidence of physician-diagnosed illnesses is simply calculated as the ratio of the number of infants with illness events to the number of infants followed. The duration of illnesses will be characterized with appropriate descriptive statistics. Conventional methods of statistical significance testing will be used (Rothman and Boice 1979; Kleinbaum et al. 1982).

Initially, stratification will be used to control confounding and to assess exposure-response relations. Standard methods described by Rothman and Boice (1979) and by Kleinbaum and coworkers (1982) will be used for the incidence data. To assess exposure-response relations with the cumulative incidence data, the Mantel extension test can be used. We are unaware of an analogous test for the incidence-rate data. Analysis of variance will be used for the duration-of-illness variable.

For the cumulative incidence measures of occurrence and for the duration-of-illness variables, conventional modeling approaches are already available. For the former, multiple logistic regression can be used to assess predictors of one or more episodes during the study period. For the duration-of-illness data, conventional multiple linear regression will be used, though transformation of the dependent variable may be necessary.

Analysis Based on Temporally Varying Exposure

Because measurements of NO_2 will be made with a two-week averaging time, we will assign NO_2 exposures to consecutive two-week intervals, beginning with entry into the study. We will also identify the subjects' status for important covariates (breast-feeding and day care) during each two-week period. Each illness event will be related to the exposure for the interval in which it occurs. Calculation of incidence rates is straightforward, as in the case of cumulative exposure.

The incidence density data, regardless of the type of exposure information, can also be analyzed with a modeling approach using Poisson regression (Frome and Checkoway 1985). This method, a multivariate approach that is conceptually similar to linear and logistic multiple regression, models the incidence densities within strata defined by exposure and covariates. We can fit this model using a SAS computer program published by Frome and McLain (1984).

The results of Poisson regression analysis are shown in Tables 34 and 35 for the hypothetical data set. We have used a multiplicative model:

$$\ln(\lambda) = \beta_0 + \sum_{i=1}^{k} \beta_i \chi_i$$

The deviances for the models are provided in Table 34; the deviance for Model 4 is not statistically significant, and Model 4 does fit the data better than Model 3 ($\chi^2 = 6.50$, $p < 0.05$). The magnitude of effect is estimated by the regression coefficient and the corresponding odds ratio.

DISCUSSION

INTRODUCTION

These pilot studies were performed in preparation for a cohort pilot study of respiratory infections and NO_2 exposure in infants. The studies had the dual purposes of establishing the feasibility of the proposed cohort study and of obtaining data needed to guide the development of the cohort study. The pilot studies were not designed to test specific hypotheses; accordingly, small sample sizes limit the interpretation of the results of some of the component projects. Nevertheless, the pilot studies provided new information concerning the characteristics of homes in the Southwest and concentrations of NO_2 in these homes. The time-activity patterns of infants were described and an approach for estimating the personal exposures of infants to

Table 33. Hypothetical Data to Illustrate Data Analysis Procedures, Second Pilot Study

Number of Illness Events	Number of Biweekly Observation Periods	NO_2 Stratum	Breast-Feeding	Incidence Rate/ Two-Week Period	Incidence Rate/Year
343	7,060	Low	No	0.049	1.26
362	6,670	Low	Yes	0.054	1.41
279	3,080	Moderate	No	0.091	2.36
345	3,140	Moderate	Yes	0.110	2.86
447	2,760	High	No	0.162	4.21
559	3,290	High	Yes	0.170	4.42

Table 34. Poisson Regression Analysis of Hypothetical Data, Second Pilot Study

Model Number	Terms in Model	Number of Parameters	Deviance	Degrees of Freedom
1	Intercept only	1	597.82	5
2	Intercept Breast-feeding	2	584.07	4
3	Intercept Moderate NO_2 High NO_2	3	8.51	3
4	Intercept Breast-feeding Moderate NO_2 High NO_2	4	2.01	2

NO_2 was developed. We also developed a surveillance system for respiratory illness in infants, and in implementing this system, we gained experience with the problems of establishing specific clinical diagnoses of respiratory illness in this age group. We will discuss the results of the two pilot studies separately, and then address the overall implications of the results for the cohort study.

FIRST PILOT STUDY

Phase 1

The principal objectives of this phase were to establish that sufficient infants could be enrolled and that the distribution of NO_2 concentrations in Albuquerque homes was appropriate for an investigation of the health effects of this pollutant. With regard to the first objective, we found that either in-hospital screening or telephone contact could be used to identify eligible infants. We could not establish the numbers of eligible infants that could be routinely identified, because recruitment was fully implemented for only one month. We were also able to compare two enrollment strategies: direct contact in the hospital and telephone call following delivery. We learned that telephone contact was more efficacious in identifying eligible subjects who subsequently participated. Though unexpected, we think that this pattern reflects the greater stability of the mothers who did not move immediately after delivery.

With regard to the second objective, we found that the distribution of NO_2 levels in Albuquerque homes followed the pattern observed elsewhere; most electric-stove homes had low levels of NO_2, and the distribution of concentrations in gas-stove homes extended beyond the present National Primary Ambient Air Quality Standard. We concluded that, at least in the winter, a strong gradient of NO_2 concentration prevails in Albuquerque homes, and that this community is an appropriate site for the cohort study.

The NO_2 concentrations in the homes with gas stoves covered a wide range (Figures 2 through 5). This finding implies that estimation of personal exposures on the basis of source descriptions alone will not provide sufficiently valid estimates of exposure for the proposed cohort study. The high correlation between activity-room concentrations and bedroom concentrations suggests that monitoring of both rooms may be unnecessary over a two-week integrating time (Table 6). The high intercycle correlation implies that monitoring every two weeks would provide little additional information on winter-time exposure. However, the greater variability of concentrations in homes with high NO_2 levels indicates that monitoring the homes with high levels more frequently than the homes with low levels may be a more efficient and informative strategy.

Table 35. Coefficients and Standard Errors for the Best-Fitting Model

Variable		$\beta \pm$ SE	Odds Ratio (95% confidence interval)
Intercept		3.886 ± 0.001	
$MODNO_2$ =	1 for moderate NO_2 0 otherwise	0.668 ± 0.002	1.95 (1.94, 1.96)
$HIGHNO_2$ =	1 for high NO_2 0 otherwise	1.169 ± 0.002	3.22 (3.20, 3.24)
BFEED =	1 if breast-feeding 0 if not breast-feeding	0.106 ± 0.001	1.112 (1.105, 1.118)

Phase 2

In Phase 2, we described concentrations of potentially confounding pollutants in homes from the upper and lower tails of the distribution of NO_2 levels. We also examined time-activity patterns of infants and determinants of their personal exposures to NO_2.

With regard to the first objective, the high-NO_2 homes and the low-NO_2 homes showed no differences in levels of respirable particles, formaldehyde, or water vapor. Analysis of the composition of the particles showed high concentrations of silicon and calcium in the indoor samples; this pattern may reflect the dustiness of homes in a desert climate, or perhaps the use of baby powder. We concluded that monitoring these potentially confounding pollutants will not be necessary in all homes in the cohort study. Monitoring formaldehyde or respirable particles in selected homes may be informative. For example, if the sample includes a sufficient number of mobile homes, we might measure formaldehyde in the mobile homes and in a sample of conventional homes.

The air-exchange rates were lower in the Albuquerque homes (Figure 7) than in homes sampled throughout the United States (Mage and Gammage 1985). Homes in Albuquerque, which has grown rapidly since World War II, tend to be newer than those in nationwide samples. Tighter construction in newer homes may partially explain the low air-exchange rates. Furthermore, multistory construction is infrequent in Albuquerque; the effect of buoyancy in increasing air exchange is greater in multistory vertical structures than in horizontally constructed single-story houses. The meteorology during the time that the measurements were made also may partially explain the low air-exchange rates. During the winter months, wind speeds are generally low and the nighttime inversions are severe.

The accuracy of the measurements of air-exchange rate must also be considered. The home volume measurements may have been incorrect in some cases, and average temperature was estimated by averaging maximum and minimum temperature. In a few homes, review of the individual air-exchange rates suggests that the assumption of uniform mixing throughout the home was violated. Nevertheless, we conclude that Albuquerque homes tend to have generally low air-exchange rates.

The study of time-activity patterns documented the overwhelming importance of indoor domestic exposures for infants who do not attend day care and whose mothers do not work outside the home. Bedroom and activity room NO_2 concentrations were the primary determinants of an infant's personal exposure. In the one-day assessment, personal exposure was satisfactorily predicted by combining area measurements with the time-activity pattern. Because of the time-activity patterns of these infants, they received most NO_2 exposure in the bedroom (65 percent) and in the activity room (32 percent), while the kitchen (5 percent) and outdoor environments (2 percent) contributed only a small fraction of daily exposure. However, we documented the occurrence of short-term peaks of NO_2 in the kitchen during cooking that would not be captured by measurements integrated over two-week periods. Thus, we conclude that concentrations measured with Palmes tubes can be used to reconstruct the infant's exposure to NO_2 when averaging times are several days to several weeks in length. However, this approach may underestimate the exposures received if the infant is in the kitchen during periods of cooking.

Phase 3

In this phase, we tested the proposed illness surveillance system and considered methods for validating the calendar-diary reports against a more conventional clinical assessment. With regard to the calendar-diary, we demonstrated that mothers will fill it out daily as requested, at least over a three-month period. The nurse practitioner confirmed that the child considered ill by its mother was nearly always ill when evaluated clinically (Table 17). Thus, we demonstrated that calendar and telephone reports of illness are valid.

We also learned that reports of respiratory illness are quite nonspecific for infants. With the calendar-diary approach, we can describe symptom complexes that overlap, but are not identical with, the usual clinical syndromes (Table 19). We concluded that the larger cohort study should incorporate assessment by a clinician, at least for a sample of cases.

SECOND PILOT STUDY

Recruitment

Our experience with a single pediatric practice suggests that subjects might be most efficiently enrolled by establishing a group of practices that would cooperate with the study. Physicians have expressed an interest in the project because of a willingness to support research and to obtain the results of virological cultures.

Exposure Assessment

In Phase 2 of the first pilot study, we showed that an infant's personal exposure can be adequately characterized by area measurements. Accordingly, this pilot study addressed the feasibility of several strategies for the placement and return of tubes, and exposure characterization was not emphasized. Some participants successfully followed protocols, but others did not (Table 24). A telephone call was not adequate for assessing compliance. In a larger study, we would rely on participants to place and return tubes only after they had demonstrated compliance, as assessed by drop-in visits. Some households will inevitably require technician visits for monitoring.

With regard to monitoring strategy, more variation was evident in homes with higher levels of NO_2 (Figure 10). This finding, also noted in the first pilot study, implies that monitoring should be performed more often in homes with higher concentrations. With regard to temporal variation in individual homes, changes in NO_2 concentrations were generally smooth, although some abrupt increases and decreases were observed, particularly in homes with higher levels (Figure 10). This pattern of variation also supports more frequent monitoring of homes with higher levels.

Surveillance

The second pilot study provided additional opportunity to refine the respiratory illness surveillance system. An assessment of the utility of this respiratory surveillance system for a large population study of infant respiratory illness must consider the system's feasibility, validity, and completeness. The feasibility of the system depends on the mothers' willingness to cooperate with study procedures and the level of staff support needed to collect accurate data. Validity is determined by the system's sensitivity and specificity in disease classification and the influence of varying population characteristics on identification or classification of disease. Completeness can be evaluated by comparing this method to other methods of measuring respiratory illness.

As before, lack of a standard for comparison posed a difficult barrier in validating our approach. Infants present an array of nonspecific signs to parents and to clinicians; even serology and culture do not identify the etiology of all illnesses. Furthermore, observers may differ in their interpretation of the clinical data, and signs may rapidly change as the illness evolves.

The two pilot studies demonstrated that our surveillance system is a feasible approach for measuring the occurrence of respiratory illness in a large population. Mothers were highly compliant in completing the calendars and in reporting symptoms and physician visits when called by a study staff member. Asking parents to initiate calls when a child was ill was not successful. In addition, the strong effect of ethnicity, Hispanic compared with non-Hispanic white, on calling behavior could lead to biased ascertainment of illness. Asking mothers to give postcards to their pediatricians at the time of visits for illness was also unsuccessful. In the cohort study, we will obtain physician diagnoses by review of medical records.

Little information on the optimal frequency for making telephone surveillance calls has been published. Tager and Speizer (1976) followed 162 schoolchildren for 10 weeks, calling the parents of half the children every 2 weeks and the parents of the other half every 4 weeks. They found no differences in the ascertainment of illnesses between the two groups, except that parents in the biweekly surveillance group were more likely to initiate calls. Overall respiratory illness rates were similar in the two groups, although children whose parents were called biweekly tended to have more reports of lower respiratory illnesses. The present study suggests that more discrete symptoms are detected when parents are called weekly (Table 27), but shows no difference in the number of parent-initiated calls.

The choice of calling frequency must be based on feasibility as well as on completeness of reporting. In the second pilot study, one staff person spent approximately seven hours each week to complete calls to 26 study respondents, an average of 16 minutes per call. In an investigation of 600 infants, four full-time staff members would be required to make biweekly surveillance calls. Doubling the workload to make weekly calls does not appear warranted even though higher symptom rates were obtained with the weekly calls.

We have found our surveillance system to be sensitive in detecting signs of illness. For this surveillance system, we assumed a priori that the symptoms of wet cough and wheeze were more likely to represent episodes of lower respiratory illness. If the nurse practitioner's clinical diagnosis is taken as the reference standard, our system has 80 percent sensitivity and 64 percent specificity. This assessment of validity is inherently limited, however, by using a clinical diagnosis as the "gold standard." Though the presence of rales or of wheezing on auscultation is highly predictive of lower respiratory illness, the absence of these signs at the time of the examination cannot exclude lower respiratory tract involvement. Lower respiratory illness in a child is a constantly evolving constellation of signs and symptoms. In milder cases of lower respiratory illness, particularly, the specific clinical diagnosis may vary with the timing of the clinical evaluation during the course of illness.

Similarly, the results of viral cultures are not an appropriate reference standard for documenting infection. Our viral isolation rate was 33 percent overall, but was 26 percent when the cytomegalovirus, poliovirus, and trichomonas isolates were excluded. Although lower than the 42 percent viral isolation rate reported in the North Carolina day care study (Loda et al. 1972) in which children were examined daily, our isolation rate is comparable to the rate of 25.6 percent in the Tecumseh study (Monto and Cavalaro 1971) and to the rate of 28 percent in the North Carolina pediatric practice study (Glezen and Denny 1973).

The completeness of ascertainment by our surveillance system can be assessed by comparing the incidence rates obtained with this system with rates obtained in other investigations. The North Carolina day care study yielded an annual incidence rate of 9.6 respiratory infections per child for children under one year of age (Loda et al. 1972). Annual rates of 8.8 total respiratory illnesses and 1.0 lower respiratory illness per child were reported by the Houston Family Study (Gardner et al. 1984). In the Tecumseh study, the annual rates were 6.1 total respiratory illnesses and 1.8 lower respiratory illnesses per child (Monto and Ullman 1974). In our study, the annual incidence of wet cough and wheeze syndromes combined was 2.6 per child, somewhat higher than the rates of lower respiratory illness in the other studies. The higher rates in our study reflect the nonspecificity of wheeze and cough for lower respiratory illness. In interpreting the annualized incidence rates from our study, consideration must also be given to extrapolation from a three-month season to an entire year.

Overall, the results of the second pilot study documented that a surveillance system for respiratory illness that incorporates calendar-diaries and biweekly telephone calls is a feasible, relatively unbiased, and sensitive method for studying respiratory illness in a large population of infants. The discrepancies between the surveillance system and conventional clinical assessment are inherent. In fact, surveillance studies that include similar methods have provided much of our current information on the epidemiology of respiratory illnesses. This type of system remains the most feasible approach for assessing the effects of NO_2 exposure on the respiratory illness experience of infants.

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Nitrogen Dioxide and Respiratory Infection: Pilot Investigations

Jonathan M. Samet and John D. Spengler

INTRODUCTION

In the summer of 1983, the Health Effects Institute (HEI) issued a Request for Applications (RFA 83-2) soliciting proposals on "Nitrogen Oxides and Susceptibility to Respiratory Infections." In September 1983, Dr. Samet, in collaboration with Dr. Spengler, proposed a project entitled "Nitrogen Oxides and Respiratory Infection in Infants." The HEI asked Dr. Samet to conduct two pilot studies to test the feasibility of the full-scale study and to develop and assess methods to be used. The first pilot study began in September 1984, the second in February 1986. Total expenditures were $283,328 for the two projects. The Investigators' Report of the two pilot studies was received at the HEI in January 1988, and was accepted by the Health Review Committee in October 1988.

During the review of the Investigators' Report, the Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Review Committee's Commentary. The Commentary is intended to place the Investigators' Report in perspective, as an aid to the sponsors of the HEI and to the public. The Commentary does not discuss the full-scale study which is now under way; rather, it provides an overview of the pilot studies as separate preliminary projects.

THE CLEAN AIR ACT

The Environmental Protection Agency (EPA) sets standards for motor vehicle emissions of oxides of nitrogen (and other pollutants) under Section 202 of the Clean Air Act, as amended in 1977. Section 202(a)(1) directs the Administrator of the EPA to "prescribe (and from time to time revise) . . . standards applicable to the emission of any air pollutant from any class or classes of new motor vehicles or new motor vehicle engines, which in his judgment cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health or welfare." Sections 202(a)(3) and 202(b)(1) impose specific requirements for reductions in motor vehicle emissions of oxides of nitrogen (and other pollutants), and provide the EPA with limited discretion to modify those requirements.

The determination of the appropriate standards for emissions of oxides of nitrogen depends, in part, on an assessment of the risks to health they present. An epidemiological study that determines whether indoor exposures to oxides of nitrogen are associated with increased susceptibility to respiratory infection can contribute knowledge useful in evaluating health effects in humans, which is an important part of informed regulatory decision-making under Section 202.

In addition, Section 109 of the Clean Air Act provides for the establishment of National Ambient Air Quality Standards. The current standards include primary and secondary standards for nitrogen dioxide, which were last reviewed in 1985. Also, under Section 166 of the Act, in February 1988, the EPA published proposed regulations to prevent significant deterioration of air quality due to emissions of oxides of nitrogen. Research of the type described here will contribute to the planning and conduct of future research used to assess the appropriateness of the existing standards, and of ongoing and future regulatory initiatives.

BACKGROUND

Nitrogen dioxide present in the air of urban environments is derived largely from vehicular sources. Morning rush-hour traffic generates high concentrations of nitric oxide which, in the presence of oxygen and sunlight, is converted to nitrogen dioxide (Ehrlich 1980). The current National Ambient Air Quality Standard for nitrogen dioxide is 0.053 parts per million (ppm) averaged over one year. Although the nitrogen dioxide standard is being met generally, hourly peaks in urban areas sometimes exceed 0.3 ppm (U.S. Environmental Protection Agency 1985). Nitrogen dioxide generated indoors by appliances such as gas stoves reaches average levels of 0.025 ppm, although peaks as high as 0.2 to 0.4 ppm may be attained (Samet et al. 1987).

Humans exposed to 1 to 2 ppm nitrogen dioxide exhibit symptoms of cough, chest tightness, and substernal irritation (Linn et al. 1985). Animal studies using these same concentrations provide clear evidence of bronchial epithelial injury down to the small airways of the lung (Evans 1984). Nitrogen dioxide exposure to 2.5 ppm or greater produces increased susceptibility to bacterial infection in a variety of animal species. In addition, low levels of nitrogen dioxide have also been shown to cause decreased immunological responses, increased levels of lung proteolytic enzymes and peptides, and hematological disturbances (see reviews by U.S. Environmental Protection Agency 1982, 1986; Morrow 1984; Samet et al. 1987; Pennington 1988).

Controlled clinical studies have sought to correlate nitrogen dioxide exposures with measures of pulmonary function in healthy and asthmatic human subjects. A review of the literature by Shy and Love (1980) concluded that earlier clinical studies collectively revealed no significant reduction in pulmonary function in normal subjects who intermittently exercised for two hours or less during exposure to nitrogen dioxide concentrations below 1.5 ppm. More recently, however, research in this area has produced conflicting evidence of health effects in asthmatic and normal subjects exposed to nitrogen dioxide levels ranging from 0.1 to 4 ppm (Ahmed et al. 1982, 1983; Hazucha et al. 1983; Kleinman et al. 1983; Linn et al. 1985; Avol et al. 1986; Morrow and Utell 1989). Little clinical work with human subjects has been done to correlate nitrogen dioxide exposure with respiratory infection (Kulle 1988).

Because epidemiological studies represent realistic human exposure situations, they may provide direct evidence for an effect of nitrogen dioxide on respiratory infections. Specific groups for study have been identified as those exposed to high concentrations of nitrogen dioxide, such as residents of homes with gas-fueled stoves, or unvented gas or kerosene heaters, urban traffic police or toll collectors, and children in areas of high ambient concentrations of nitrogen dioxide.

In evaluating whether or not nitrogen dioxide exposure increases susceptibility to, or severity of, respiratory infection, exposure and outcome variables must be assessed accurately and confounding factors must be measured. Accurate exposure assessment can best be accomplished by measuring personal exposure to nitrogen dioxide. Although the average ambient levels of nitrogen dioxide can be determined readily, the relation of such levels to personal exposures is difficult to assess. Recent advances in monitoring technology have made it possible to collect, in field settings, measurements of personal exposure that are integrated over days or weeks; however, assessment of short-term personal exposures remains difficult (Ryan et al. 1988; Sexton and Ryan 1988).

To evaluate the health outcome of nitrogen dioxide exposure, clinical examinations combined with microbiological testing would be an appropriate method to diagnose respiratory infections; but these methods are time-consuming and expensive. Differentiation among types of symptoms, for example, between asthmatic cough and infectious cough, is often imprecise, and the isolation of respiratory infection-producing viruses is a relatively inefficient process (Monto et al. 1985; Denny and Clyde 1986). For the purposes of large-scale surveys or to assess past illnesses, questionnaires are often the most practical means of gathering the needed information. However, questionnaires are susceptible to many sources of error, such as recall bias, random error introduced by poor recall, and imprecise interpretation of medical terminology. Thus, it may be difficult to determine the severity, as well as the duration, of respiratory infections through questionnaires. In addition, confounding factors such as age, smoking habits, socioeconomic status, day-care use, family size and composition, and exposure to other air pollutants, may obscure a true association, or account for a spurious association, between measured nitrogen dioxide concentrations and incidence of respiratory infections.

It has been shown that residents who use gas cooking stoves are subject to higher average indoor nitrogen dioxide exposures than those who use electric stoves (National Research Council 1981). Several epidemiological studies have compared respiratory symptoms and exposure histories of schoolchildren who live in homes with gas stoves with those of schoolchildren who live in homes with electric stoves. Melia and collaborators (1977) published one of the first reports of adverse health effects associated with the use of gas cooking stoves. They surveyed the respiratory symptoms and illnesses of 5,758 schoolchildren in England and Scotland. Using an outcome variable composed of diverse symptoms and diseases, they found significantly higher prevalences of bronchitis, cough, and chest colds in children living in homes with gas stoves than in those living in homes with electric stoves. Because the analysis did not control for the potentially important confounding effects of parental smoking or socioeconomic status, the results are not readily interpretable. In a later study, Melia and coworkers (1982) measured nitrogen dioxide levels in 183 homes. After analyses that controlled for age, sex, social class, and parental smoking, no statistically significant associations were found between the nitrogen dioxide levels and the prevalence of the composite respiratory illness variable.

Ogston and coworkers (1985) studied gas-stove use and respiratory illness during the first year of life in 1,565 infants born in Dundee, Scotland. The incidence of respiratory illness was higher for infants in homes with gas stoves than for children from homes with electric stoves, but the difference was not statistically significant. In a large retrospective study of children ages six to ten, Speizer and coworkers (1980a,b) found a small, but statistically significant, association between the current use of a gas stove and a history of respiratory illness before the age of two. When the data from this study were adjusted for socioeconomic status (Ware et al. 1984), the estimated odds ratio of 1.23 ($p < 0.01$) for respiratory illness was reduced by 30 percent and was no longer significant.

Only a few studies have looked at the association between gas-stove use and respiratory infection in adults. In a survey of 1,724 residents of Washington County, MD, Comstock and associates (1981) found an increased frequency of respiratory symptoms in men (nonsmokers) who live in homes with gas stoves compared to men who live in electric-stove homes. In contrast, Keller and associates (1979) monitored the incidence of respiratory illness in 441 upper-middle-class families in Ohio through twice-weekly telephone calls and random sampling of nitrogen dioxide levels of homes. They found no statistically significant association between respiratory illness and gas-stove use.

Studies of other nitrogen dioxide-exposed groups have not clarified the link between nitrogen dioxide levels and incidence of respiratory infections. In a comparison of urban police, who are exposed to high concentrations of nitrogen dioxide from automobile exhaust, with suburban traffic police, Speizer and Ferris (1973a,b) found no differences in the frequency or types of respiratory symptoms between the two groups. A study of schoolchildren living in areas with high levels, compared with low levels, of nitrogen dioxide was undertaken in Chattanooga, TN (Shy et al. 1970a,b). Postcard surveys of health status and weekly ventilatory function revealed more respiratory symptoms and influenza in the children living in the high-nitrogen dioxide area; however, independent review later revealed serious shortcomings in the study design and the nitrogen dioxide measurements (Ferris 1978).

Overall, the results of the epidemiological studies are inconclusive as to whether or not nitrogen dioxide exposure is associated with increased susceptibility to, or severity of, respiratory illness. Most studies have produced only limited, and unvalidated, information on either nitrogen dioxide exposure, health outcome, or both.

JUSTIFICATION FOR THE STUDY

Relatively high doses of nitrogen dioxide can cause serious toxic effects, but whether or not ambient levels of nitrogen dioxide exposure present risks to health is uncertain. The HEI solicited proposals that would help resolve the issue of whether or not exposure to nitrogen dioxide at or near the ambient exposure range enhances susceptibility to, or increases the severity of, respiratory infections. An association between nitrogen dioxide exposure and respiratory infections was of particular interest to the HEI because the current nitrogen dioxide standard is based, in part, on the epidemiologic study in Chattanooga (Shy et al. 1970a,b), but the questions raised by this study have not been resolved by subsequent research.

In response to the RFA, Dr. Samet and coworkers proposed to test the hypothesis that exposure to nitrogen dioxide increases the occurrence of respiratory infections in infants during the first year of life. The proposed study focused on the effects of nitrogen dioxide generated from gas cooking stoves in the homes of nonsmokers residing in Albuquerque. One thousand infants born in two large Albuquerque hospitals were to be enrolled in the study, drawn equally from homes with and without gas stoves. The HEI Research Committee found a high degree of scientific merit in the proposed study; however, the Committee decided that the plans for the study should be pilot-tested in a small sample population to assess the feasibility of conducting the full study.

GOALS AND OBJECTIVES

Two separate pilot studies were conducted. The specific aims of the first pilot study were (1) to determine the feasibility of enrolling a sufficient number of eligible infants in the proposed full-scale study; (2) to measure concentrations of nitrogen dioxide in Albuquerque homes with gas or electric stoves; (3) to measure concentrations of potentially confounding pollutants in homes with the highest and lowest levels of nitrogen dioxide; (4) to develop methods for estimating personal exposures of infants to nitrogen dioxide, including assessment of the infants' time-activity patterns; and (5) to pilot test the proposed approach to illness surveillance.

The specific aims of the second pilot study were (1) to enroll infants and evaluate their recruitment, using labor and delivery room logs, from the University of New Mexico Hospital, the Lovelace Medical Center, and a pediatric medical practice; (2) to evaluate methods for measuring exposure to nitrogen dioxide, including measuring nitrogen dioxide variation by integrated two-week monitoring in 15 homes, and to test a strategy for mailing passive nitrogen dioxide monitoring devices (Palmes tubes) to the 15 homes; (3) to monitor respiratory illnesses for three months with calendar-diary records and telephone calls, clinical evaluations by a nurse-practitioner, and viral cultures and fluorescent antibody stains of throat and nasopharyngeal swabs from sick children and a sample of well children; and (4) to develop and test plans for data analysis in the full-scale study.

TECHNICAL EVALUATION

ATTAINMENT OF STUDY OBJECTIVES

The investigators successfully achieved their objectives. The valuable information obtained through completion of the pilot studies was useful in planning the full-scale study.

DISCUSSION OF METHODS AND INTERPRETATION OF RESULTS

Both pilot studies were well conducted, and the Investigators' Report provides a clear description of the procedures and results. The investigators established that there is a gradient of exposure to nitrogen dioxide in Albuquerque among infants from homes with gas stoves, when compared with homes with electric stoves. The results suggest that recruitment of an adequate sample for the full-scale study is feasible. Methods for measuring exposure and health outcomes were carefully assessed.

Infant Recruitment

Although fewer than 5 percent of the eligible women who were contacted refused to participate, only 14 percent of those screened in the hospital and only 21 percent of those screened by telephone actually participated in the first pilot study. Mothers' cigarette smoking constituted the principal reason for ineligibility for enrollment in the study (36 to 40 percent). In the second pilot study, the goal was to recruit a total of 75 infants in three weeks at a rate of 25 per week, and to achieve a 7:3 ratio of gas-stove homes to electric-stove homes; it actually took seven weeks to reach the total number. The final yield from screening in the second pilot study was 11.2 percent, whereas it was 16.3 percent in the first pilot study. However, the second study used slightly different methods and less stringent criteria for eligibility; it also included a private pediatric medical practice.

Overall, the recruitment of infants was low; for the full study, it is likely that additional sources of infants will be needed to assure recruitment of sufficient numbers. It is also uncertain what the participation rates will be when surveillance continues for a longer period. Limiting the study to infants of nonsmoking mothers is an appropriate way to eliminate one of the known determinants of respiratory infections; however, reliance on questionnaires to determine environmental tobacco smoke exposure may not be sufficient to contol for this confounding variable.

Certain characteristics of the infants and of the households in which they live are known to be related to infection rates, and this information should be collected and included in the analyses. Birthweight, length of gestation, and information on all other household members, including the ages and genders of other children, should be ascertained (information about gestational age, breast-feeding, and day-care use was obtained in the second pilot study).

Day care is a variable of considerable interest, particularly as it relates to infant infection rates. In the second pilot study, a brief questionnaire that included information on day care was administered during the first nurse-practitioner visit. The results of the survey are not presented; however, day-care use was an exclusion criterion in the second pilot study, and it was decided that infants spending more than 20 hours per week in day care would not be enrolled in the full-scale study. Also, appropriately, the effect of day-care use is to be analyzed as a covariate in the final analyses.

An association between gas stoves and lower socioeconomic status (low incomes and less parental education) was noted in both pilot studies. If differences in infection rates are found between infants from the two types of homes, the contribution of socioeconomic status to the differences will need careful consideration in the full study.

Illness Surveillance

Documentation of the incidence of respiratory illnesses will be central to the success of the full-scale study. Therefore, a major objective of the pilot studies, particularly the second, was to corroborate the information gathered by the primary illness surveillance method, the calendar-diary.

The information on infants' health collected by the calendar-diary, filled out daily by the mother, was cross-checked with information collected by four other methods: (a) nurse-practitioner visit to the household at the time of illness, initiated by a telephone call from the mother; (b) biweekly phone calls to the mother by the nurse-practitioner; (c) postcards given to the mother to be filled out by the pediatrician at the time of an illness visit; and (d) characterization of infection by viral cultures, performed on a sample of ill children and a random sample of well children. This verification scheme was designed to address several problems commonly associated with reliance on respiratory illness information derived from questionnaires completed by parents.

Descriptions of illness by parents and trained clinicians are not always consistent. Therefore, parental reports of symptoms and illness were compared with nurse-practitioner diagnoses and, although not always correlated, were found to be more accurate for severe types of infection (lower respiratory tract infections) than for minor symptoms. In addition, if a mother said that chest symptoms were absent, then lower respiratory tract infection was almost never diagnosed by a physician or nurse-practitioner. The fact that parents were found to identify lower respiratory tract infection correctly should enable targeting the home visits for clinical assessment and viral cultures in order to verify episodes of lower respiratory tract infection.

Parental compliance with established protocols is important for the conduct of a study. It is unfortunate, therefore, that mothers did not consistently call study personnel to report new respiratory illnesses in their children (nor were the postcards consistently filled out by pediatricians). The full-scale study will ask for compliance from parents for 18 months, significantly longer than the three-month period surveyed in the pilot studies. The biweekly surveillance calls led to useful responses, and will have to be relied upon. Maintaining parental compliance (and, if possible, increasing it) throughout the full study will be important.

Clinical examination by medical personnel may be the most widely accepted measure of illness, but it is time-consuming and expensive. The investigators ascertained the effectiveness of verifying respiratory infection by virologic testing. The virus cultures were obtained from one well child for every third child (later, every second child) with lower respiratory tract infection. Although this protocol (used in Pilot Study II) appears to be the most objective method for diagnostic measurement, it established viral etiology of illness in only 35 percent of ill children. This rate of virus isolation is comparable to rates found in other studies (Loda et al. 1972; Glezen and Denny 1973; Monto et al. 1985). Although it is generally believed that most respiratory illnesses among infants are viral in origin, the reasons for the poor rate of virus isolation are not fully understood (Monto et al. 1985; Denny and Clyde 1986).

The results of the Pilot Studies suggest that symptoms and signs of respiratory tract infections occur commonly enough and can be ascertained reliably enough for there to be adequate numbers of events during the projected observation period. The results also indicate that the best approach to illness surveillance may not be reliance on one method alone; rather, a combination of methods that would allow verification of the parent-completed calendar-diary and comparisons among the methods may be more desirable. Attention must be given to determinants of infection rates (child's age, gender, prior lower respiratory tract infection, household size and composition, and environmental tobacco smoke, among others) that may confound the comparisons of illness between children from homes with gas stoves and those from homes with electric stoves. However, when the incidence rates in this study were extrapolated to one year, they were comparable to those reported in other surveillance studies (Loda et al. 1972; Monto and Ullman 1974; Gardner et al. 1984).

Exposure Assessment

Levels of indoor and outdoor pollutants, relative humidity, and home ventilation rates were obtained with state-of-the-art methods. In homes with gas stoves surveyed in the first pilot study, two-week average levels of nitrogen dioxide frequently exceeded the National Ambient Air Quality Standard of 53 parts per billion (ppb), whereas such levels were found in only one home with an electric stove—a house with an unvented gas furnace. However, the levels of indoor and outdoor nitrogen dioxide concentrations were lower in the second pilot study. Mean values in infants' bedrooms were 33 and 31 ppb (two separate sampling cycles) for gas-stove homes in the first pilot study and 30 and 23 ppb in the second pilot study; in contrast, the nitrogen dioxide concentrations in infants' bedrooms in the electric-stove homes were 7 and 6 ppb for Pilot Study I, and 7 and 4 ppb for Pilot Study II. Pilot Study II was conducted between January and March, 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 levels in Pilot Study II. Correlations between indoor and outdoor nitrogen dioxide levels were quite high for both gas-stove homes and electric-stove homes during the pilot studies.

Potentially confounding pollutants, such as particulates and heavy metals, were measured in 49 homes and found to be correlated with outdoor levels; no differences between homes with high-nitrogen dioxide levels and homes with low-nitrogen dioxide levels were reported. Formaldehyde was monitored in activity rooms in a sample of 11 homes. Week-long passive sampling revealed a total mean of 0.05 ppm formaldehyde, with no measurement above 0.1 ppm. The authors concluded that monitoring formaldehyde will not be necessary unless many mobile homes are included in the study; however, 11 homes may constitute too small a sample to assess the need to measure this pollutant. Volatile organic compounds were not evaluated; some information would have been desirable to determine whether they have any effect on respiratory infections.

The strategy for monitoring nitrogen dioxide was successful: 92 percent of potential Palmes tube samples were obtained, and data were judged complete and valid for 85 percent of them. Although technician-placed samplers led to data of the highest quality, all households to which tubes were mailed provided at least one set of valid data. These results indicate that nitrogen dioxide levels can be monitored most effectively when technicians place and retrieve the tubes. Reliance on parents to place and return the tubes over the lengthy period of the full-scale study will require long-term commitment by the parents and may be problematic.

Within the gas-stove homes, the levels of nitrogen dioxide were found to vary substantially, between 0 and more than 150 ppb. It is not clear if monitoring homes with high-nitrogen dioxide levels more frequently than homes with low-nitrogen dioxide levels, as the authors have suggested, would reveal any additional information. Because of the high level of variability observed in high-nitrogen dioxide homes, it is not known how many observations in a gas-stove home will be required before it can be considered a high-, versus a low-, nitrogen dioxide home. Ideally, it would be desirable not to classify homes into two discrete types and to model respiratory infection as a function of nitrogen dioxide concentration measured as a continuous variable, with a wide range of nitrogen dioxide represented. However, if it is necessary to limit the number of observations made, it may be better to monitor all homes less frequently, rather than to classify a home as a high- or low-nitrogen dioxide home early in the course of the study and then to base monitoring frequency on that possibly erroneous assessment.

The full-scale study has the potential for evaluating the effect of exposure to nitrogen dioxide on infection and illness rates in young children. The relatively high correlations between outdoor and indoor nitrogen dioxide levels suggest that, even in homes with gas stoves, outdoor pollution contributes to indoor nitrogen dioxide levels. However, effects of exposure from gas stoves may differ from effects due to outdoor sources, such as automotive sources, because short-term peaks occur during cooking. If peak exposures have different effects than long-term lower concentration exposures, the study may not fully capture or quantify such an association if nitrogen dioxide concentrations are averaged over two-week intervals. Furthermore, exposures to nitrogen dioxide among the exposed infants may not be sufficiently high, or the variability in exposure may not be large enough, for this investigation to demonstrate an association between nitrogen dioxide exposure and susceptibility to respiratory infections if there is such an association. However, it is noteworthy that the range of exposures found in the pilot studies is appropriate to provide information relevant to the current annual National Ambient Air Quality Standard.

DATA ANALYSIS

The Data Analysis section of the Investigators' Report discusses the methods of statistical analyses that may be used in the full-scale study, which is appropriate because the small sample sizes used for the pilot studies precluded actual testing of the hypotheses.

The investigators are experienced in analyzing data from cohort studies, and have considered a variety of measures of exposure and of outcome. Confounding factors will be controlled using traditional approaches. Exposure-outcome relationships will be assessed by stratified analyses, multiple logistic regression, and Poisson regression. These methods of analyses are appropriate for both the cross-sectional and the longitudinal data that will be gathered.

The day-to-day sampling variability in nitrogen dioxide within homes, and the home-to-home variability within each group, may be explored by components of variance analysis. These analyses may be useful in optimizing the nitrogen dioxide sampling design by showing the relative sizes of these sources of variation.

CONCLUSIONS

The methodological advances of the two pilot studies represent a substantial accomplishment and will be useful to others. The studies provide information about state-of-the-art methods for monitoring indoor exposure to nitrogen dioxide and for characterizing respiratory illnesses and infections in infants. The Review Committee's Commentary is confined to the Pilot Studies; it was not the intention of the Review Committee to evaluate the features of the full-scale study design.

The effect of nitrogen dioxide exposure on respiratory infections is an important subject for HEI-supported research. Epidemiologic evidence for an association between nitrogen dioxide and respiratory infections or illnesses is, as yet, equivocal, having been derived from studies with methodological limitations, including the use of crude or surrogate measures of exposure and inadequate characterization of respiratory infections. We anticipate that the full-scale study, now in progress, will provide reliable information about the effect of low levels of exposure to nitrogen dioxide on the susceptibility of infants to respiratory infections.

As the pilot study methodologies are applied to the full-scale study, some obstacles are sure to be encountered. For example, the demands of the the full-scale study will impose a substantially greater burden on the involved mothers and, to a lesser extent, on the other members of their families and on their pediatricians; attention and effort will be required to keep them motivated. The consistently excellent performance of the technical staff, instruments, and measurement techniques also will be essential to collecting high-quality data to establish the credibility of the results, which may play an important role in assessing the National Ambient Air Quality Standard for nitrogen dioxide.

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Special Reports

Title	Publication Date
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research	September 1985
Automotive Methanol Vapors and Human Health: An Evaluation of Existing Scientific Information and Issues for Future Research	May 1987
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research (Supplement)	January 1988

Research Reports

Report No.	Title	Principal Investigator	Publication Date
1	Estimation of Risk of Glucose 6-Phosphate Dehydrogenase-Deficient Red Cells to Ozone and Nitrogen Dioxide	M. Amoruso	August 1985
2	Disposition and Metabolism of Free and Particle-Associated Nitropyrenes After Inhalation	J. Bond	February 1986
3	Transport of Macromolecules and Particles at Target Sites for Deposition of Air Pollutants	T. Crocker	February 1986
4	The Metabolic Activation and DNA Adducts of Dinitropyrenes	F.A. Beland	August 1986
5	An Investigation into the Effect of a Ceramic Particle Trap on the Chemical Mutagens in Diesel Exhaust	S.T. Bagley	January 1987
6	Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate on Metabolic and Pulmonary Function	D.M. Drechsler-Parks	April 1987
7	DNA Adducts of Nitropyrene Detected by Specific Antibodies	J.D. Groopman	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
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11	Effects of Ozone and Nitrogen Dioxide on Human Lung Proteinase Inhibitors	D.A. Johnson	August 1987
12	Neurotoxicity of Prenatal Carbon Monoxide Exposure	L.D. Fechter	September 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
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Report No.	Title	Principal Investigator	Publication Date
17	Studies on the Metabolism and Biological Effects of Nitropyrene and Related Nitro-polycyclic Aromatic Compounds in Diploid Human Fibroblasts	V.M. Maher	March 1988
18	Respiratory Infections in Coal Miners Exposed to Nitrogen Oxides	M. Jacobsen	July 1988
19	Factors Affecting Possible Carcinogenecity of Inhaled Nitropyrene Aerosols	R.K. Wolff	August 1988
20	Modulation of Pulmonary Defense Mechanisms Against Viral and Bacterial Infections by Acute Exposures to Nitrogen Dioxide	G.J. Jakab	October 1988
21	Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoxide at Several Altitudes	S.M. Horvath	December 1988
22	Detection of Paracrine Factors in Oxidant Lung Injury	A.K. Tanswell	February 1989
23	Responses of Susceptible Subpopulations to Nitrogen Dioxide	P.E. Morrow	February 1989
24	Altered Susceptibility to Viral Respiratory Infection During Short-Term Exposure to Nitrogen Dioxide	R.M. Rose	March 1989
25	Acute Effects of Carbon Monoxide Exposure on Individuals with Coronary Artery Disease	HEI Multicenter CO Study Team	To be released soon
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. Heinrich	May 1989
27	Cardiovascular Effects of Chronic Carbon Monoxide and High-Altitude Exposure	J.J. McGrath	July 1989

Copies of these reports can be obtained by writing to the Health Effects Institute, 215 First Street, Cambridge, MA 02142.

THE HEALTH EFFECTS INSTITUTE: AN OVERVIEW

The Health Effects Institute (HEI) is an independent nonprofit corporation that is "organized and operated . . . to conduct, or support the conduct of, and to evaluate research and testing relating to the health effects of emissions from motor vehicles." It is organized in the following ways to pursue this purpose.

INDEPENDENCE IN GOVERNANCE

The Institute is governed by a four-member Board of Directors whose members are Archibald Cox (Chairman of the Board), Carl M. Loeb University Professor (Emeritus) at Harvard University; William O. Baker, Chairman (Emeritus) of Bell Laboratories and Chairman of the Board of Rockefeller University; Donald Kennedy, President of Stanford University; and Charles Powers, Partner, Resources for Responsible Management.

TWO-SECTOR FINANCIAL SUPPORT

The Institute receives half of its funds from the United States government through the Environmental Protection Agency, and half from the automotive industry. Twenty-seven domestic and foreign manufacturers of vehicles or engines contribute to the Institute's budget in shares proportionate to the number of vehicles or engines that they sell.

THE HEI RESEARCH PROCESS

The Institute is structured to define, select, support, and review research that is aimed at investigating the possible health effects of mobile source emissions. Its research program is developed by the Health Research Committee, a multidisciplinary group of scientists knowledgeable about the complex problems involved in determining the health effects of mobile source emissions. The Committee seeks advice from HEI's sponsors and from other sources prior to independently determining the research priorities of the Institute.

After the Health Research Committee has defined an area of inquiry, the Institute announces to the scientific community that research proposals are being solicited on a specific topic. Applications are reviewed first for scientific quality by an appropriate expert panel. Then they are reviewed by the Health Research Committee both for quality and for relevance to HEI's mission-oriented research program. Studies recommended by the Committee undergo final evaluation by the Board of Directors, who review the merits of the study as well as the procedures, independence, and quality of the selection process.

THE HEI REVIEW PROCESS

When a study is completed, a final report authored by the investigator(s) is reviewed by the Health Review Committee. The Health Review Committee has no role either in the review of applications or in the selection of projects and investigators for funding. Members are also expert scientists representing a broad range of experience in environmental health sciences. The Committee assesses the scientific quality of each study and evaluates its contribution to unresolved scientific questions.

Each Investigator's Report is peer-reviewed, generally by a biostatistician and three outside, independent reviewers chosen by the Review Committee. At one of its regularly scheduled meetings, the Review Committee discusses the Investigator's Report. The comments of the Committee and the peer reviewers are sent to the investigator, and he or she is asked to respond to those comments and, if necessary, revise the report. The Review Committee then prepares its Commentary, which includes a general background on the study, a technical evaluation of the work, a discussion of the remaining uncertainties and areas for future research, and implications of the findings for public health. After evaluation by the HEI Board of Directors, the HEI Research Report, which includes the Investigator's Report and the Review Committee's Commentary, is then published in monograph form. The Research Reports are made available to the sponsors, the public, and many scientific and medical libraries, and are registered with NTIS.

All HEI investigators are urged to publish the results of their work in the peer-reviewed literature. The timing of the release of an HEI Research Report is tailored to ensure that it does not interfere with the journal publication process.

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