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NITROGEN DIOXIDE

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Nitrogen dioxide (NO_2) causes lung damage at high concentrations (Lowry and Schuman 1956; National Research Council [NRC] 1976), but effects at levels currently encountered in outdoor and indoor air have been difficult to characterize. Early epidemiologic studies focused on the health effects of ambient NO_2 (Shy et al. 1978). Few investigations directed at NO_2 exposure from ambient sources have involved populations exposed primarily to NO_2 (NRC 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 evidence from studies of persons exposed to NO_2 in outdoor air or in the workplace cannot be extended to the indoor environment.

Studies conducted during the 1970s in the laboratory and in homes showed that indoor combustion sources were adding NO_2 and nitric oxide (NO) to indoor air and that indoor concentrations often exceeded outdoor concentrations in many homes (NRC 1981). The predominant role of indoor sources in determining personal exposure to nitrogen oxides was quickly recognized. Consequently, more recent epidemiologic studies have emphasized sources and effects of indoor NO_2 concentrations.

Combustion processes generate NO and, to a lesser extent, NO_2 (NRC 1976). Nitric oxide, however, is converted to NO_2, the nitrogen oxide of principal concern with regard to health in indoor environments. Combustion processes may also produce other potentially toxic derivatives of the nitrogen oxides such as nitric acid and nitrates, but the extent of these compounds in indoor air and their effects on health have not been addressed.

NO_2 is an oxidant gas that is soluble in tissues. Dosimetric studies show that most inhaled NO_2 is retained in the lungs and deposited primarily in the large and small airways, with little deposition in the alveoli (Goldstein et al. 1980; Miller et al. 1982). Because of its degree of tissue solubility, NO_2 reacts not only with the alveolar epithelium, but also with the interstitium and endothelium of the pulmonary capillaries (Mustafa and Tierney 1978). Inhaled NO_2 is thought to combine with water in the lung to form nitric (HNO_3) and nitrous (HNO_2) acids (Goldstein et al. 1980; Overton and Miller 1988), although substantial uncertainty remains concerning the tissue reactions to NO_2 (Morrow 1984).

Oxidant injury has been postulated to be the principal mechanism through which NO_2 damages the lung (Mustafa and Tierney 1978). At high concentrations, NO_2 causes extensive lung injury in animals and in humans (NRC 1976). Fatal pulmonary edema and bronchopneumonia have been reported at extremely high concentrations; lower concentrations are associated with bronchitis, bronchiolitis, and pneumonia (NRC 1976; Morrow 1984).

Experimental evidence indicates that NO_2 exposure adversely affects lung defense mechanisms (Gardner 1984; Morrow 1984). Lung defense mechanisms against inhaled particles and gases include aerodynamic filtration, mucociliary clearance, particle transport and detoxification by alveolar macrophages, and local and systemic immunity. In experimental models, 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 (NRC 1976; Dawson and Schenker 1979; Gardner 1984; Morrow 1984; Pennington 1988). The results of some experimental models, however, have not implied adverse effects of NO_2 on lung defenses (Lefkowitz, McGrath, and Lefkowitz 1986; Mochitate et al. 1986).

In animal experiments involving challenge with respiratory pathogens, exposure to NO_2 reduces clearance of infecting organisms and increases the mortality of the experimental animals (Dawson and Schenker 1979; Jakab 1980; Morrow 1984; Pennington 1988). In these infectivity models, the pathogens have most often been bacteria although viruses have also been used. 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; NRC 1976; Pennington 1988). Adverse effects have generally been demonstrated at concentrations an order of magnitude greater than generally found in indoor environments. Investigators at the U.S. Environmental Protection Agency have conducted a series of experiments to assess the consequences of various exposure patterns. These studies indicate that for short-term exposures, concentration has a greater effect on susceptibility than duration (Gardner et al. 1982), and the adverse effects of short-term spikes of exposure may be biologically significant (Miller et al. 1987). The studies with spikes of exposure may parallel the general

pattern of human exposure to NO_2 from indoor sources, as short-term peak exposures can result from appliances used during cooking or space heating.

EXPOSURE

In the home environment, the principal combustion sources of NO_2 include gas stoves, gas water heaters, and space heaters. Central gas furnaces are vented to the outside and release little NO_2 into a home unless the venting system is malfunctioning. Automobile exhaust containing NO_2 may enter a home from an attached garage, and tobacco smoking also produces NO_2. The air of commercial buildings may be contaminated with NO_2 from entrained exhaust and from tobacco combustion. In locations with higher concentrations of NO_2 in ambient air, the entry of outdoor air into indoor environments elevates indoor concentrations further.

Combustion of gas during cooking and the burning of pilot lights releases NO, NO_2, carbon monoxide (CO), carbon dioxide (CO_2), and water (NRC 1981). On average, normal use of an unvented gas cooking range adds 25 parts per billion (ppb) NO_2 to the background concentration in a home (Spengler et al. 1983). The distributions of NO_2 levels in homes with gas and electric cooking ranges are distinct but overlap to some extent (Figure 7.1). The increase is greater during cold weather when the air exchange rate is usually reduced. Use of a gas stove or oven for space heating, a common practice in some cities in cold climates, results in particularly high concentrations of NO_2 (Sterling, Dimich, and Kobayashi 1981). During cooking with a gas range, peak levels in the kitchen may reach 200–400 ppb (Spengler and Sexton 1983), and measured personal exposures to NO_2 are therefore higher for persons living in homes with gas stoves than for persons living in homes with electric stoves (Quackenboss et al. 1982; Yocom 1982; Spengler et al. 1983).

Exposure to NO_2 from gas cooking stoves and ovens is widespread. About 50 percent of homes in the United States have gas cooking appliances; in some urban areas, such as Los Angeles, more than 90 percent of homes are equipped with gas appliances (U.S. Bureau of the Census 1983). The potential importance for health of indoor exposure to NO_2 is underscored by a comparison of the federal standard set for ambient air, 50 ppb annual average, with the levels measured in homes with gas cooking appliances. For example, Spengler and co-workers (Spengler et al. 1983) measured NO_2 in 137 homes in Portage, Wisconsin, a rural community with extremely low ambient levels of NO_2. The annual mean levels in the kitchens exceeded the present national ambient air quality standard in 10 percent of the homes with gas stoves. Sexton and co-workers (Sexton, Letz, and Spengler 1983) used data generated by personal, indoor, and outdoor monitoring to develop a computer model for personal and indoor exposure. The model was applied to residents of six U.S. cities. Although none of the cities experienced NO_2 concentrations in outdoor air above the federal standard (50 ppb), the model predicted that more than 25 percent of the residents of homes with gas ranges would have annual personal exposures above the level of the standard if ambient NO_2 concentrations averaged 30 ppb. Furthermore, persons in a kitchen during cooking with a gas stove may receive short-term exposures at concentrations substantially above the annual standard for ambient air.

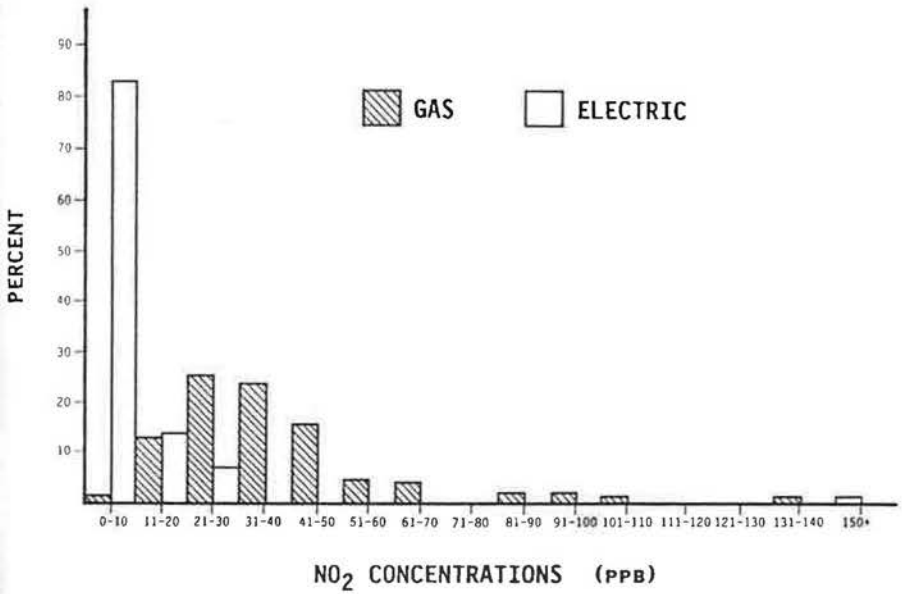

Figure 7.1. Two-week integrated NO_2 concentrations in the activity room in homes in Albuquerque, New Mexico. *Source:* Marbury et al. (1988), reprinted with permission.

The use of space heaters, which produce heat by combustion, may also increase the level of exposure to NO_2. Gas-fired space heaters that are not vented to the outside emit NO, NO_2, and CO (NRC 1981). Unvented kerosene space heaters, increasingly popular for home heating since the energy crises of the 1970s, produce NO_2, CO, and sulfur dioxide (SO_2) (Leaderer 1982; Traynor et al. 1985). In a study of Connecticut homes, the presence of a kerosene space heater and the pattern of its use were strong determinants of NO_2 concentrations measured during the winter (Leaderer et al. 1987). In fourteen homes in the South with unvented gas space heaters, NO_2 concentrations exceeded the ambient standard of 50 ppb in eleven of the fourteen homes during a four-day monitoring period (McCarthy, Yarmac, and Yocom 1987).

HEALTH EFFECTS

To date, studies on the health effects of exposure to NO_2 in indoor air have only addressed exposure in the home environment. Most of these studies have focused on respiratory symptoms and illnesses and on the level of pulmonary function.

Experimental investigations support the choice of these outcome measures: NO_2 may damage the lung directly through its oxidant properties or indirectly by increasing susceptibility to respiratory infections (NRC 1976; Jakab 1980).

Data on the health effects of NO_2 concentrations likely to be encountered by the general population are derived from experimental and epidemiologic studies. The results of some human exposure studies imply that levels comparable to those measured in homes may increase the level of airways reactivity in some asthmatics, but the results of other studies are inconsistent (Orehek et al. 1976; Bauer et al. 1984; Morrow 1984; Bromberg 1988). Although experimental studies are useful for describing effects of acute exposures in specific populations, they cannot address the issue of chronic effects from chronic lower level exposures. Numerous epidemiologic investigations that provide evidence on the health effects of NO_2 in indoor environments have now been carried out.

The majority of these investigations are cross-sectional surveys of schoolchildren (Tables 7.1 and 7.2). The investigators generally assessed current symptom status and retrospective illness histories, as obtained by parent-completed questionnaire, and pulmonary function. Although NO_2 levels were measured in several of the investigations (Florey et al. 1979; Melia et al. 1982; Fischer et al. 1985), exposure was most often assessed by simple questions concerning type of fuel used for cooking. Consistent evidence of excess respiratory symptoms and illnesses in children exposed to gas stoves has not been demonstrated (Table 7.1).

Early reports from two cross-sectional surveys of schoolchildren in Great Britain indicated that children from homes with gas stoves had a higher prevalence of respiratory symptoms than children from homes with electric stoves (Melia et al. 1977; Melia, Florey, and Chinn 1979). When one of the survey groups was followed longitudinally, however, the relative risks associated with gas stove use became highly variable and tended to decrease as the children grew older (Melia, Florey, and Chinn 1979). These same British investigators surveyed a third group of 808 schoolchildren and measured NO_2 concentrations in the homes of a small sample ($N = 80$ or 103). The prevalence of respiratory symptoms was higher in children from homes in which gas was used for cooking and increased with higher bedroom NO_2 concentrations although both effects were of borderline statistical significance (Florey et al. 1979). A similar association between measured NO_2 and respiratory symptoms was not replicated, however, when these same investigators subsequently studied another sample of 183 children (Melia et al. 1982). Two prospective studies of infants in Great Britain also failed to demonstrate an association between the use of gas for cooking and respiratory illness (Melia et al. 1983; Ogston, Florey, and Walker 1985).

Data on children from the United States are similarly inconsistent. Two large cross-sectional studies, one involving the Harvard Six-Cities study (Speizer et al. 1980a, 1980b) and the other involving schoolchildren in Iowa (Ekwo et al. 1983), have demonstrated that reports of serious respiratory illness before age two (Speizer et al. 1980a, 1980b) and hospitalization for respiratory illness before age two (Ekwo et al. 1983) were more common among children from homes with gas

Table 7.1 Effects of Gas Cooking on Respiatory Illnesses and Symptoms in Children

Study Population	Outcome Measure	Results
British Studies		
5,758 children, aged 6–11 years, England and Scotland (Melia et al. 1977)	Major respiratory symptoms and diseases individually and as a single composite variable describing the presence of any one of six symptoms or diseases	Significant associations with gas cooking of selected symptoms and diseases, and of a composite variable
2,408 children, 42% of original 5,758 in above study (Melia, Florey, and Chinn 1979)	Single composite variable as described above	Relative risk for composite variable generally exceeded 1.0; risk varied and decreased with age
4,827 children, ages 5–11 years, England and Scotland (Melia, Florey, and Chinn 1979)	Single composite variable as described above	Significant effect of gas stoves on composite variable in urban areas only
808 children, aged 6–7 years, United Kingdom (Florey et al. 1979)	Single composite variable as described above	Borderline significant association between composite variable and gas stoves; increased prevalence as bedroom NO_2 levels increased in a sample with measurements ($N = 80$)
191 children, aged 5–6 years, England (Melia et al. 1982)	Single composite variable as described above	No significant association between bedroom NO_2 levels and prevalence of composite variable
390 infants, aged 0–1 years, England (Melia et al. 1983)	Respiratory illnesses and symptoms requiring physician visits, assessed prospectively	No association between gas stove use and respiratory illnesses and symptoms
1,565 infants, aged 0–1 years, England (Ogston, Florey, and Walker 1985)	Respiratory illnesses and hospitalizations assessed prospectively to 1 year	No significant association between illness or hospitalizations and use of gas for cooking
Ohio Studies		
441 upper-middle-class families including 898 children under age 16 (Keller et al. 1979a)	Incidence of acute respiratory illness, determined by biweekly telephone calls	Respiratory illness incidence similar in homes using gas and electric stoves
120 families from first study, including 176 children under age 12 (Keller et al. 1979b)	Incidence of acute respiratory illness, determined by biweekly telephone calls and validated by home visits	Respiratory illness incidence similar in homes using gas and electric stoves
Harvard Six-Cities Study		
8,120 children, aged 6–10 years, six U.S. cities (Speizer et al. 1980a,	History of physician-diagnosed bronchitis or serious respiratory illness	Significant association between current use of gas stove and history of res-

(*continued*)

Table 7.1 (*Continued*)

Study Population	Outcome Measure	Results
1980b)	before age 2 or respiratory illness in last year	piratory illness before age 2; odds ratio = 1.23
10,106 children, aged 6–10 years, six U.S. cities; expansion of above study (Ware et al. 1984)	Same as above	Odds ratio for history of respiratory illness before age 2 decreased to 1.2; $p = .07$)
6,273 children, six U.S. cities, 1983–86 sample (Dockery et al. 1987)	Same as above, and chronic cough and persistent wheeze	No significant associations; odds ratio for respiratory illness before age 2 years was 1.09; 95% CI[a] 0.89, 1.33
Other Studies		
676 children, third and fourth grades, Arizona (Dodge 1982)	Prevalence of asthma, wheeze, sputum, cough as determined by parent-completed questionnaire	Significant association between use of gas stove and prevalence of cough; prevalence rate ratio = 1.97
4,071 children, aged 5–14 years, Pennsylvania (Schenker, Samet, and Speizer 1983)	Major respiratory illnesses and symptoms as determined by parent-completed questionnaire	No significant association between use of gas stove and any symptom or illness variable
1,138 children, aged 6–12 years, Iowa (Ekwo et al. 1983)	Major respiratory symptoms and illnesses as determined by parent-completed questionnaire	Significant association between current gas stove use and hospitalization for respiratory illness before age 2; odds ratio = 2.4
121 children, aged 0–13 years, Connecticut (Berwick et al. 1984)	Number of days of illness	Number of days of illness associated with average hours of space heater use
231 children, aged 6 years, The Netherlands (Hoek et al. 1984)	Comparison of NO_2 levels in homes of cases (children with asthma) and controls	NO_2 distributions similar in homes of cases and controls

[a]Confidence interval.

stoves. When the original cohort in the Harvard six-cities study was expanded, however, the odds ratio of 1.23 for serious respiratory illness before age two decreased to 1.12 ($p = 0.07$). More recently, the Harvard group enrolled a new sample of preadolescent children ($N = 6,273$) in the same six cities (Dockery et al. 1987). In this new population of children, exposure to a gas stove was not significantly associated with any respiratory symptoms or doctor-diagnosed chest illness before age two years. In the Iowa study (Ekwo et al. 1983), the effect of exposure to a gas stove varied strongly and inconsistently with parental smoking habits. The effect was absent in homes where one parent smoked, largest where both parents smoked, and intermediate where neither smoked. This pattern of interaction cannot be readily interpreted biologically. Schenker and colleagues (Schenker, Samet, and Speizer 1983) found no association between the type of cooking stove and

Table 7.2 Effects of Gas Cooking on Lung Function in Children

Study Population	Lung Function Measure	Results
808 children, aged 6–7 years, United Kingdom (Florey et al. 1979)	PEFR, $FEV_{0.75}$, FEF_{25-75}	No association with NO_2 levels or presence of gas stove
898 children, aged 0–15 years, from 441 families, Ohio (Keller et al. 1979a)	FVC, $FEV_{0.75}$	Data on children not presented separately; no association with presence of a gas stove
8,120 children, aged 6–10 years, six U.S. cities (Speizer et al. 1980a, 1980b)	FVC, FEV_1	Overall reduction of 16 and 18 ml, respectively, for FEV_1 and FVC in children from homes with gas stoves
16,689 children, aged 6–13 years, seven areas in U.S. (Hasselblad et al. 1981)	$FEV_{0.75}$	Significant reduction of 19 ml associated with gas stove use in older girls only
676 children, third and fourth grades, Arizona (Dodge 1982)	FEV_1	No effect of gas stoves on pulmonary level or rate of growth
183 children, aged 6–12 years, Iowa (Ekwo et al. 1983)	FEV_1, FEF_{75}, FEF_{25-75}	No change after isoproterenol challenge in children from homes with gas stoves
9,720 children, aged 6–10 years, six U.S. cities (Ware et al. 1984)	FEV_1, FVC	Significant reduction in FEV_1, of 0.6% and FVC of 0.7%; not significant after adjustment for parental education
3,175 children, aged 5–14 years, Pennsylvania (Vedal et al. 1984)	FVC, $FEV_{0.75}$, FEF_{25-75}, $\dot{V}_{max\,75}$, $\dot{V}_{max\,90}$	No association with use of gas stove

current respiratory symptoms or previous illness history in a cross-sectional survey of 4,071 schoolchildren in western Pennsylvania.

The relationship between stove type and respiratory illness has also been studied prospectively. Keller and colleagues (Keller et al. 1979a, 1979b), in a study of 1,952 family members of all ages in Ohio, found that respiratory illness incidence did not vary with stove type. More recently, Berwick and co-workers (Berwick et al. 1984) followed 121 children for three months, 59 from homes with kerosene heaters and 62 from homes without such heaters. In a preliminary analysis of their data, they found that hours of heater use, which correlated strongly ($r = .70$) with one-week integrated NO_2 measurements, was significantly associated with the occurrence of illness lasting for one or more days.

The data concerned with lung function level in children are similarly inconclusive (Table 7.2). Of the four investigations with large sample sizes (Speizer et al. 1980a; Hasselblad et al. 1981; Vedal et al. 1984; Ware et al. 1984), two have demonstrated small but statistically significant effects of exposure to a gas stove (Speizer et al. 1980a; Hasselblad et al. 1981). In initial cross-sectional analysis of data from the Harvard Six-Cities Study, Speizer and co-workers (Speizer et al. 1980a) demonstrated average reductions, adjusted for parental smoking and socioeconomic status, of 16 and 18 ml in the FEV_1 and the FVC, respectively, in

children from homes with gas stoves compared with children from homes with electric stoves. On expansion of the cohort, however, the reductions in FEV_1 and FVC, although still statistically significant, were 0.6 percent of predicted for the former and 0.7 percent for the latter (Ware et al. 1984). With adjustment for parental education, the effects of exposure to a gas stove were reduced by 30 percent and were no longer statistically significant. Cross-sectional analysis of lung function data collected at the children's second examination did not show significant effects of stove type. With extension of the follow-up interval the investigators assessed determinants of pulmonary function growth and found no effect of gas stove exposure (Berkey et al. 1986).

Hasselblad and colleagues (Hasselblad et al. 1981) analyzed data from the Environmental Protection Agency's Community Health Environmental Surveillance System. They reported that in girls ages nine to thirteen years gas stove exposure decreased $FEV_{0.75}$ by an average of 18 ml after adjustment for parental educational level and smoking status. An effect was not observed in girls ages six to eight years nor in boys ages six to thirteen years.

In another large cross-sectional study, Vedal and colleagues (Vedal et al. 1984) examined the effects of stove type on spirometric volumes and flow rates in a sample of 3,175 children ages five to fourteen years. With adjustment for parental smoking and socioeconomic status, exposure to a gas stove was not significantly associated with reduced lung function level.

The effects of gas stove exposure on lung function level were assessed in five other investigations, but the sample sizes were inadequate for detecting effects of the magnitude found in the larger studies. Keller and co-workers (Keller et al. 1979a) performed spirometry on one occasion in a sample of the subjects in their surveillance study. The data were not reported separately for children, and overall there was no effect of stove type. In one of the cross-sectional surveys conducted in Great Britain, the investigators correlated lung function level with one-week measurements of NO_2 in the kitchen and in the children's bedrooms (Florey et al. 1979). With a sample of about four hundred children, significant effects of NO_2 were not found. Dodge (1982) and Ekwo and colleagues (Ekwo et al. 1983) did not find effects of stove type on lung function measures in their cross-sectional studies. Hosein and Corey (1984) examined the influence of nine indoor factors on FEV_1 in 1,357 nonsmoking white children from three U.S. towns. Their preliminary report indicated that exposure to gas stoves was significantly associated with a 0.148-liter reduction in FEV_1 level in boys and a 0.75-liter reduction in girls.

Only a few investigations provide data on acute and chronic effects of NO_2 exposure indoors on adults (Table 7.3). Prospective studies of acute respiratory illness occurrence have not demonstrated excesses in residents of homes with gas stoves (Keller et al. 1979a, 1979b; Love et al. 1982). Cigarette smoking and chronic respiratory diseases, potential confounding variables, were not considered in these studies.

Potential chronic effects have also been examined in populations of adults (Table 7.3). Comstock and co-workers (Comstock et al. 1981) reported that gas stove use

Table 7.3 Effects of Gas Cooking on Pulmonary Illness, Symptoms, and Function of Adults

Study Population	Outcome Measure	Results
441 upper-middle-class families, including 1,054 adults over 15 years, Ohio (Keller et al. 1979a)	Incidence of acute respiratory illness, determined by biweekly telephone calls	Respiratory illness incidence similar in homes using gas and electric stoves
120 families from first study, including 269 adults over 18 years, Ohio (Keller et al. 1979b)	Incidence of acute respiratory illness, determined by biweekly telephone calls and validated by home visit	Respiratory illness incidence similar in homes with gas and electric stoves
1,724 adults, aged >20 years, Maryland (Comstock et al. 1981)	Major chronic respiratory symptoms, FEV_1, FVC	Association between gas stove use and increased prevalence of respiratory symptoms, FEV_1 <80% predicted, FEV_1/FVC <70%, found in nonsmoking males only
708 adults, aged >20 years; nonsmoking sample of above population (Helsing et al. 1982)	Major chronic respiratory symptoms, FEV_1, FVC	Significant association between gas stove use and increased prevalence of chronic cough and phlegm, low FEV_1/FVC
102 nonsmoking women in lowest quartile of FEV_1 compared with 103 nonsmoking women in highest quartile, Michigan (Jones et al. 1983)	Comparison of proportions of cases and controls currently using gas stoves	Marginal association between use of gas stove and lower lung function; odds ratio = 1.8, p = .08
97 nonsmoking adult females, Netherlands (Fischer et al. 1985)	IVC, FEV, FVC, PEF, MEF_{75}, MEF_{25}, MMEF	Cross-sectional analysis showed an association between current NO_2 exposure and decreases in most pulmonary function measures; no association with longitudinal decline in pulmonary function

was associated with a significantly increased prevalence of certain chronic respiratory symptoms and of ventilatory impairment in nonsmoking men but not in smoking men or in women of either smoking status. A subsequent reanalysis limited to the never and former smokers showed significant increases in chronic cough and phlegm and in the prevalence of low FEV_1/FVC in association with gas stove use in both sexes (Helsing et al. 1982).

In a study of ninety-seven nonsmoking rural women from The Netherlands, personal exposure estimates were created by combining one-week measurements of NO_2 with time-activity information (Remijn et al. 1985). The investigators demonstrated a cross-sectional association between lung function level and current NO_2 exposure but failed to show an association between retrospectively estimated

exposure to NO_2 and longitudinal decline in pulmonary function during the antecedent seventeen years (Fischer et al. 1985).

Using a case-control design, Jones and coworkers (Jones et al. 1983) compared cooking fuel exposures of twenty- to thirty-nine-year-old nonsmoking women in the highest and lowest quartiles of the lung function distribution in the Tecumseh community health study, a longitudinal study of health in Tecumseh, Michigan. The odds ratio for the effect of cooking with gas compared with electric appliances on lung function level was 1.82 ($p = .076$).

Lebowitz and colleagues (Lebowitz 1984; Lebowitz et al. 1982, 1985) have evaluated acute effects of gas stove exposure on lung function and symptoms in 229 subjects drawn from 117 Tucson households. The families were sampled from a larger study population to include persons with and without asthma, allergies, and airway obstruction. During a two-year period, subjects completed symptom diaries and monitored their peak flow daily. Multivariate analyses indicated adverse effects of gas stoves on symptoms and peak flow rate in asthmatics but not in normal subjects (Lebowitz et al. 1985). However, the magnitude of the effect is difficult to determine from the available publications.

Recently, Kasuga and colleagues (Kasuga 1985) proposed that the urinary hydroxyproline to creatinine ratio is a valid and sensitive indicator of lung damage from environmental pollutants, including tobacco smoke and NO_2. Hydroxyproline, an amino acid constituent of collagen, is a product of collagen catabolism; therefore, an increase in its excretion reflects an increase in collagen destruction.

Matsuki and co-workers (Matsuki et al. 1984, 1985) conducted a cross-sectional study of 820 schoolchildren and their 546 mothers during both a summer and a winter period. They measured subjects' twenty-four-hour personal NO_2 exposures with filter badges and collected early morning urine samples for evaluation of the hydroxyproline to creatinine ratio. In multiple regression equations, passive smoking status and personal NO_2 were independent and significant predictors of this ratio in both schoolchildren and adult women in both seasons. Distance from a main road, as a surrogate for exposure to automobile exhaust, was found to be a stronger predictor of the ratio in summer than in winter in schoolchildren and a predictor only during the summer in adult women. A linear relationship was also found between the value of the ratio and the amount of passive exposure to tobacco smoke. Other studies, however, have not shown relationships of the hydroxyproline to creatinine ratio with either passive exposure to tobacco smoke (Adlkofer, Scherer, and Heller 1984) or with active smoking (Read and Thornton 1985). Although the hydroxyproline to creatinine ratio could serve as a useful biochemical indicator of lung injury by NO_2 exposure, further investigations are needed to clarify ambiguities in the available data.

SUMMARY

Definitive statements concerning the risk of NO_2 exposure from cooking with gas stoves and other indoor sources cannot be made at present. Although many studies have examined respiratory illnesses, respiratory symptoms, and lung function in children and adults, their results are not consistent and are not adequate for establishing a causal relationship. Retrospective illness histories may be inaccurate, and their results may be biased by whether the subjects have symptoms or illness at the time of their interview (Samet, Tager, and Speizer 1983). Variations in the characteristics of the study populations and differing end points may partly explain the differences among the studies. Confidence limits have not been uniformly presented in the studies on gas stoves, and the results of many of the smaller studies which have been judged as negative are probably consistent with the larger studies that show small effects.

Unfortunately, NO_2 exposures were measured directly in only a few investigations (Florey et al. 1979; Melia et al. 1982; Hoek et al. 1984; Fischer et al. 1985), and in all of these the measurements spanned at most two-week periods. In the other studies, categorical variables, indicating gas or electric stove use, were employed. However, neither limited area measurements nor variables for stove type tightly predict actual personal exposure (Spengler et al. 1983). Thus, the results of all the investigations of the health effects of NO_2 exposure from gas stoves are affected by random misclassification. This type of bias reduces the magnitude of the observed association from the value that would be found if the exposure of subjects was estimated correctly (Shy et al. 1978). Ozkaynak and colleagues (Ozkaynak et al. 1984) have shown that misclassification introduced by the use of a categorical variable for stove type may introduce substantial underestimation of the true relative risk values associated with the actual NO_2 exposure.

Bias from inadequate control of confounding factors must also be considered in interpreting the foregoing studies (Vedal 1985). Confounding occurs when the effect of one variable on the outcome of interest has not been separated from the effects of other variables. For example, maternal smoking has been associated with reduced lung function level in children. Confounding by maternal smoking could arise in a particular study if mothers of infants living in homes with gas stoves were more likely to smoke. With regard to NO_2 exposure from gas stoves and effects on respiratory illnesses and symptoms, and pulmonary function in children, the potential confounding variables include parental smoking, socioeconomic status, and asthma. Active smoking, occupational exposures, and the presence of chronic respiratory diseases should also be considered in adults. Control of these potentially confounding factors has been variable among published studies (Vedal 1985), and in some studies socioeconomic status has been treated as a confounding factor. However, the effect of socioeconomic status represents a summation of the effects of the associated environmental and familial factors, one of which may be gas stove exposure. Thus, control for socioeconomic status may reduce the likelihood of finding an effect of gas stove exposure.

The findings on NO_2 exposure and respiratory illnesses indicate that the magnitude of the NO_2 effect at concentrations encountered in most U.S. homes is likely to be small. Groups with particularly high exposures, such as the urban poor who heat with ovens and those who heat their homes with unvented kerosene or gas

space heaters, have not yet been investigated adequately. The evidence on respiratory symptoms and lung function level in children and adults is also inconclusive. However, because more than half of U.S. homes have gas cooking stoves and childhood respiratory illness is extremely common, even a small effect of gas stoves would assume public health importance. In order to detect associations of the anticipated small magnitude, future investigations should employ direct measurement of exposure rather than surrogate variables. Infants and other potentially susceptible groups seem the most suitable populations for study. Nevertheless, the epidemiologic evidence implies that clinically relevant effects of NO_2 from gas stoves are uncommon at the concentrations found in most U.S. homes.

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