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Respiratory Effects Associated with Indoor Nitrogen Dioxide Exposure in Children

LOUIS S PILOTTO,* ROBERT M DOUGLAS,* ROBYN G ATTEWELL AND SUSAN R WILSON†**

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Background. The human health effects of exposure to indoor nitrogen dioxide (NO_2) are unclear, and few studies have examined the effects of short-term peak levels of exposure.

Methods. The association between indoor exposure to NO_2 and respiratory illness was examined in 388 children aged 6–11 years. The NO_2 levels were monitored during winter in 41 classrooms, from four schools with unflued gas heating and four schools with electric heating. Each classroom was monitored daily with 6-hour passive diffusion badge monitors over nine alternate weeks, and with hourly monitors over two of those weeks. Children living in homes with unflued gas appliances were also monitored daily over four evenings during times of gas use.

Results. Exposure to NO_2 at hourly peak levels of the order of ⩾80 ppb, compared with background levels of 20 ppb, was associated with a significant increase in sore throat, colds and absences from school. An increase in cough with phlegm was marginally significant. Significant dose-response relationships were demonstrated for these four measures with increasing levels of NO_2 exposure.

Conclusions. Short-term peak levels of exposure are important to consider in relation to adverse respiratory effects associated with NO_2 exposure.

Keywords: nitrogen dioxide, air pollution, indoor, respiratory tract disease

Nitrogen dioxide (NO_2) is an air pollutant that is generated indoors from tobacco smoke and gas-fired stoves and heaters.[1] However, the human health effects of exposure to indoor NO_2 are unclear, due partly to inconsistent findings in past epidemiological studies.[2–16] A number of explanations have been proposed for the inconsistencies, including the absence of objective measurements of NO_2 in many studies, and the use of retrospective questionnaires to obtain illness histories.[17] However, it is also important to consider the way in which NO_2 has traditionally been measured. In past studies, Palmes tubes have been used to measure average levels of indoor NO_2 over 1–2 week periods. The question arises whether or not the use of such average levels to classify subjects is another possible explanation for the inconsistencies. Using an infectivity model, animal studies have shown that repeated exposure to short-term peaks of NO_2, especially peaks that are three to four times higher than background levels, appear to be more important in pathogenesis than total dose or absolute background level exposure.[18–21]

In Australia, gas stoves are commonly used for cooking in homes, and unflued gas heaters are a common source of indoor space heating during winter in homes and schools. Here we report on a study of respiratory symptoms in 6–11 year old children, followed prospectively through a winter period, using passive monitors, exposed daily during periods of gas use at home and at school, to estimate peak levels of NO_2 exposure.

MATERIALS AND METHODS

Passive Diffusion Badge Monitors

Passive diffusion badge monitors, manufactured and analysed in accordance with specifications laid down by the Standards Association of Australia, were used to measure atmospheric NO_2.[22] These monitors have a limit of detection of 45 ppb, with up to 10% error, for an exposure time of one hour. Monitors, including blanks, were encoded and analysed blind in weekly batches.

* National Centre for Epidemiology and Population Health, and † Centre for Mathematics and its Applications, The Australian National University, Canberra, ACT, Australia, 0200.
** Intstat Australia, PO Box 64, Ainslie, ACT, Australia, 2602.

Schools

Four schools with electric and four with unflued gas heated classrooms, paired geographically in western Sydney, were selected to participate. The school buildings were brick construction, up to two floors in height, with windows on two sides. Both the length and breadth of classrooms were approximately 10 metres, with ceilings up to 2.5 metres.

For monitoring purposes, schools were divided into two groups, each with two gas heated and two electric heated schools, providing a total of 41 classrooms. The classrooms from each group were monitored daily over nine alternate weeks between April and September 1992. For the first 7 weeks, three new monitors, placed horizontally at the front, centre and rear of each classroom approximately one metre from the floor, were exposed for the duration of each 6-hour school day. After that, the number of monitors placed in electric heated classrooms was reduced to two, since the variation between the monitor levels in previous weeks was consistently $\leqslant$20 ppb. Of the intended 9 weeks of monitoring, six classrooms were monitored on all days, 27 missed 1–2 days of monitoring, and eight classrooms missed 3–4 days. Of the days monitored, all monitors were successfully analysed from 21 classrooms, and over 95% of monitors were successfully analysed from each of the other 20 classrooms. All recorded values for each classroom were used for exposure determination. Apart from normal breaks and special activities, each child remained in the same classroom for the entire study period.

Hourly monitoring over the school day was also undertaken in each classroom over two of their monitored weeks. Twenty-five classrooms were successfully monitored on 10 days, nine on at least 8 days, and six on 6 days, with all recorded hourly values being used for exposure determination.

Two 6-hour monitors were placed in a sheltered position outside each school daily for one week.

Data Collection

In all, 1100 letters were distributed to pupils in 41 classrooms to be taken home to their parents, inviting them to participate in the study by keeping daily diaries of their children's respiratory symptoms. For ethical reasons, parents were informed that gas combustion was being investigated. Symptoms recorded daily by parents were hoarse voice, sore throat, cough with phlegm, dry cough, sneezing, stopped up nose, runny nose, and wheezing. As well, each parent recorded daily if their child had a cold or was absent from school. Symptom data collection commenced 4 weeks prior to the start of atmospheric monitoring. Each diary contained data recorded over one week, and four diaries were sent to parents every 4 weeks from March to September 1992. A rate for each symptom for each child was determined by expressing symptom days as a proportion of the number of recorded days of observation.

A short questionnaire to determine home smoking and gas use was distributed in May 1992. Subsequently, children who were exposed to gas appliances but not tobacco smoke at home were monitored over four evenings. In all, 121 children were given sealed badge monitors to take home to be opened only by their parents. Each parent was instructed by phone that the family should carry out typical evening activities and should expose and pin the badge monitor onto the outer garment of their child's clothing. Instructions were given that monitors were to be worn for one hour in homes when gas was being used for periods shorter than one hour. Otherwise the monitors were to be worn during gas use or until bedtime if gas was used longer. All times of monitor exposure were recorded.

Demographic and other background data were collected using a respiratory health questionnaire, based on the American Thoracic Society Questionnaire, Division of Lung Diseases, which was sent to each parent in September 1992. A second mailout for non-responders was conducted in December 1992. Telephone contact was subsequently used to reach as many remaining questionnaire non-responders as possible.

Statistical Analysis

The focus of the analysis was to model the possible relationships between each of the symptoms and the estimated amount of exposure to NO_2 at school and at home. Because the symptom rates were highly positively skewed, analyses were conducted initially on the logarithm of the symptom rates. Then, the proportions of children with at least one day with a particular symptom during the study period were investigated with respect to exposure to NO_2 using logistic regression.

Due to the inherent clustering of subjects, the analyses were carried out using mixed models with the fixed part of the model reflecting the amount of NO_2 exposure and the random part reflecting the clustering of children within classrooms. The estimation of the mean symptom rates and the variance components was conducted using the Residual Maximum Likelihood (REML) procedure in GENSTAT 5 Release 3.[23] The models for the dichotomized responses (presence/absence of a symptom) were also carried out in GENSTAT using the marginal method of Breslow and Clayton[24] in the generalized linear mixed model procedure (GLMM) with binomial error distribution and logit link specifications.

The methods of classification of children according to different levels of exposure are based on distributional

TABLE 1 *Overall mean 6-hour average nitrogen dioxide (NO_2) concentration for each classroom for the monitoring periods shown*

Electrically heated classrooms Mean 6-hour conc. in ppb				Unflued gas heated classrooms Mean 6-hour conc. in ppb			
Room No.	Weeks 1–3	Weeks 4–18[a]	Weeks 19–20	Room No.	Weeks 1–3	Weeks 4–18[a]	Weeks 19–20
	School 1				School 2		
1	20	20 (0)	10	6	23	65 (19)	33
2	26	23 (1)	11	7	17	50 (12)	15
3	22	21 (0)	8	8	21	65 (17)	19
4	23	23 (0)	11	9	17	72 (22)	30
5	21	23 (1)	10				
	School 3				School 4		
10	18	14 (0)	11	15	12	57 (16)	10
11	25	14 (0)	11	16	15	64 (17)	11
12	16	12 (0)	10	17	10	51 (15)	7
13	21	13 (0)	14	18	11	53 (12)	59
14	17	16 (0)	13	19	16	116 (23)	53
				20	14	31 (7)	9
	School 5				School 6		
21	18	11 (0)	7	26	14	29 (6)	7
22	16	10 (0)	7	27	14	23 (3)	11
23	17	11 (1)	6	28	17	33 (7)	12
24	16	13 (1)	5	29	16	21 (2)	5
25	17	11 (0)	7	30	15	18 (2)	4
	School 7				School 8		
31	11	8 (0)	4	36	28	132 (27)	137
32	11	8 (0)	3	37	31	77 (24)	85
33	10	7 (0)	3	38	15	60 (18)	60
34	12	8 (0)	3	39	15	101 (25)	103
35	12	8 (0)	4	40	12	72 (28)	46
				41	15	76 (25)	36

[a] Bracketed values are the number of days on which the measured NO_2 levels exceeded 40 ppb.

findings and are discussed in Results. Group differences and dose-response relationships were evaluated. The possible confounding effects of asthma, severe chest illness before the age of two, allergies and/or hayfever, geographical area (four regions), age (dichotomized as <9 and $\geqslant 9$ years) and gender were investigated by including all six confounder variables with the various exposure level terms.

Finally, possible effect modification by age, gender and health factors was assessed by fitting separate models containing interaction terms between exposure levels and age, gender, severe chest illness before the age of two, allergies and asthma.

RESULTS

The Cohort

Initial response rates were similar between children from electrically heated (76%) and unflued gas heated (78%) schools. From the 850 who agreed to participate, daily diaries were received for 635 children. Only 598 were satisfactory (16 were blank and 21 were incomplete). The drop-out rates for the 252 children were similar between the electrically heated (31%) and unflued gas heated schools (28%). A further 111 were excluded because of maternal or paternal smoking at home and 62 for failure to provide information on home smoking or gas appliance use. Thus, 425 children were available for exposure classification and analysis.

Exposure Determination

The overall mean 6-hour average concentrations for each classroom clearly showed that weeks 4–18, henceforth referred to as the winter heating period, constituted the uniform period of gas use across the gas heated classrooms (Table 1). Examination of the daily classroom 6-hour concentrations revealed a consistently low exposure level in the non-gas atmospheres of the order of ⩽20 ppb. However, 6-hour daily levels in unflued gas heated classrooms during the winter heating period ranged from similarly low levels in some classrooms in school 6 to levels >200 ppb in school 8. The range of exposures recorded for each room over the winter heating period was associated with the mean; i.e. the rooms with the highest means had the widest ranges.

Allowing for the one hour limit of detection of monitors, classrooms with maximum hourly levels >80 ppb were further examined. Maximum hourly concentrations in these classrooms each day over their 2 weeks of hourly monitoring were highly correlated with their corresponding 6-hour concentrations measured over the same 2 weeks ($r = 0.85$). The mean of the ratios of maximum one-hourly to 6-hourly averages was 2.19, with a standard deviation of 0.34. This ratio indicated that hourly peaks of NO_2 of the order of ⩾80 ppb were associated with 6-hour average levels of approximately ⩾40 ppb in unflued gas heated classrooms during the winter heating period. We infer from this that children in gas classrooms, which had 6-hour average levels of ⩾40 ppb, were experiencing one-hour peaks of exposure that were approximately fourfold or more higher than the NO_2 levels experienced by children who had no gas exposure (20 ppb). This 4:1 ratio of peak to background levels is similar to that shown to contribute to mortality in animal studies, over a range of absolute background levels.[21]

Average home exposure levels >40 ppb would likewise necessarily have involved higher peak levels. At home, children wore the monitors on their clothing. As they moved to rooms with differing NO_2 levels, peak levels at least of the order of magnitude of unflued gas classrooms would have been required to achieve the average levels that were observed on the home monitors. Because of the limited home monitoring period, the mean of the daily average levels for each household was used for classification. Of the 121 homes with unflued gas appliances, 101 recorded mean concentrations greater than 40 ppb. Of these, 32 homes experienced means greater than 40 ppb up to 80 ppb, 32 greater than 80 ppb up to 120 ppb, 26 greater than 120 ppb up to 200 ppb, and 11 greater than 200 ppb.

The NO_2 levels monitored outside each school were low. Six schools recorded mean 6-hour average outside concentrations of 10 ppb with little variation. The remaining two schools recorded outside means of 20 ppb and 30 ppb respectively, also with little variation.

Low and High Exposure Classification

Children were initially separated into low and high exposure groups using a cutpoint of 40 ppb. Children from gas appliance schools with 6-hour levels >40 ppb on at least 5 days during the winter heating period or from homes with mean levels >40 ppb were classified as having high exposure. In all, there were 244 children in this high exposure group. The low exposure group consisted of 105 children from electrically heated schools without exposure to gas combustion at home. Thirty-six children from electric schools, with measured home gas levels <40 ppb or whose homes were unmeasured, were excluded from the analysis. This avoids misclassification as limited information on home exposure makes it uncertain whether higher peak levels were experienced by these children.

There remained a group of 40 children from unflued gas heated classrooms 27, 29 and 30 where the exposure levels were consistently below the 40 ppb cutpoint. Of these, one child was exposed to home gas appliances with measured home gas levels <40 ppb, and was therefore excluded for the reason mentioned above. This left 39 children with an intermediate exposure level between the low and high exposure groups. These 39 children were excluded from the initial analyses comparing the low and high exposure groups.

In relation to symptom reporting for children included in the comparative analyses, 89% of parents maintained ⩾10 weeks of diaries during the 15 weeks of the winter heating period, and 73% had complete records throughout this period. As well, reporting of symptoms was continuous for 94% of the unexposed and 92% of the exposed and intermediate children.

Dose-Response Exposure Classification

For testing dose response, children were allocated to one of the following categories: <40 ppb, 40–60 ppb, 60–80 ppb, 80–100 ppb and >100 ppb. Each classroom was allocated to a category by the occurrence of 6-hour average levels exceeding the lower limit of the category on >5 days and not exceeding its upper limit on more than 5 days. Home levels were classified by the mean level measured for each home. The higher of these two allocations was used to determine each child's category. The 39 children classified as intermediate above were included in the dose-response analysis as an additional group halfway between the first and second groups.

Comparison of Low and High Exposure Groups

The symptom rates and the presence of symptoms for 7 weeks prior to the winter heating period were compared between the low and high exposure groups. No statistically significant differences were found for any symptom.

The mean symptom rates during the winter heading period for sore throat, colds and absenteeism were statistically significantly larger in the high NO_2 exposure

TABLE 2 *Crude geometric mean symptom rates during the winter heating period for low[a] and high[b] nitrogen dioxide (NO_2) exposure groups, and mean differences estimated from mixed models with and without adjustment for confounding,[c] but allowing for correlation between children within classrooms*

Symptom	Crude geometric mean[d] symptom rates		Mixed model (no adjustment n = 349)		Mixed model (with adjustment n = 336)	
	Low exposure n = 105	High exposure n = 244	Difference High-Low	*P*	Adj. difference High-Low	Adj. *P*
Hoarse voice	0.007	0.012	0.004	0.2	0.002	0.6
Sore throat	0.032	0.045	0.010	0.08	0.014	0.03
Cough with phlegm	0.037	0.062	0.025	0.01	0.020	0.06
Dry cough	0.067	0.079	0.014	0.2	0.002	0.9
Sneeze	0.027	0.029	0.002	0.8	0.006	0.4
Stopped up nose	0.053	0.054	0.001	0.9	0.000	1.0
Runny nose	0.077	0.074	–0.004	0.7	–0.012	0.3
Wheeze	0.007	0.016	0.009	0.08	0.009	0.2
'Cold'	0.041	0.068	0.027	0.007	0.028	0.01
Absent from school	0.014	0.024	0.010	0.004	0.010	0.01

[a] Low exposure ⩽40 ppb NO_2.
[b] High exposure >40 ppb NO_2.
[c] Confounders include asthma, early severe chest illness, allergies/hayfever, geographical area, age (<9/9+), gender.
[d] ln (rate + 1) was used since some rates were zero.

group than in the low exposure group (Table 2). The unadjusted rates were also higher for cough with phlegm, but the difference decreased with adjustment for confounding. For all symptoms except runny nose, there was a pattern of higher symptom rates in the high exposure group.

The pattern of proportions of children with at least one symptom during the winter heating period in the high and low exposure groups (Table 3) was similar to that of the mean rates (Table 2). The odds ratio (OR) for absenteeism for high versus low NO_2 exposure was statistically significantly greater than one, whereas the OR for runny nose was statistically significantly lower.

Dose-Response Analysis

Statistically significant positive dose-response trends were found for *mean rates* for cough with phlegm (Figure 1 $P = 0.02$ unadjusted, $P = 0.04$ adjusted for confounders), absences from school ($P = 0.01$ unadjusted, $P = 0.02$ adjusted) and sore throat (but only after adjustment for confounding $P = 0.01$). Statistically significant positive dose-response relationships were also found for the *proportions* of children with colds ($P = 0.03$ unadjusted, $P = 0.07$ adjusted), absent from school ($P = 0.0004$ unadjusted, $P = 0.002$ adjusted) and with sore throats (but only after adjustment for confounding $P = 0.03$). Figures 2 and 3 show the unadjusted dose-response relationships for the proportions of children with colds and absenteeism.

Effect Modification

A statistically significant interaction term between exposure level and chest illness before the age of two was found for hoarse voice symptom rates ($P = 0.046$). An association with exposure was only seen for children with a history of chest illness (adjusted mean rates: high exposure 0.024 versus low exposure 0.005).

Statistically significant interactions were found for both mean symptom rates ($P = 0.02$) and proportions ($P = 0.02$) for dry cough and gender. Exposure was associated with dry cough in boys (adjusted OR = 2.37; 95% [confidence interval] CI : 1.02–5.53) but not girls (adjusted OR = 0.61; 95% CI : 0.29–1.29). On the other hand an interaction in the opposite direction ($P = 0.05$) was found for colds; (adjusted OR = 2.27; 95% CI : 1.14–4.52 for girls and adjusted OR = 0.80; 95% CI : 0.36–1.81 for boys).

DISCUSSION

Exposure to NO_2 at hourly peak levels of the order of ⩾80 ppb (and average levels often exceeding 40 ppb), compared with background levels of 20 ppb, was associated with a significant increase in rates of sore throat, the presence of a cold and absence from school. Cough

TABLE 3 *Crude proportions of children in low[a] and high[b] nitrogen dioxide (NO_2) exposure groups with at least one symptom day recorded during the winter heating period, and odds ratios for presence of symptoms (high vs low exposure) and 95% confidence intervals (CI) estimated with and without adjustment for confounding[c] in Generalized (binomial) Linear Mixed Models (GLMM) allowing for correlation between children within classrooms*

Symptom	Exposure groups: Proportion with symptoms		High versus low exposure: Unadjusted (n = 349)		Adjusted for confounders (n = 336)	
	Low (n = 105)	High (n = 244)	OR	(95% CI)	OR	(95% CI)
Hoarse voice	0.21	0.28	1.49	(0.86–2.58)	1.29	(0.71–2.37)
Sore throat	0.64	0.67	1.14	(0.71–1.85)	1.39	(0.80–2.41)
Cough with phlegm	0.49	0.57	1.44	(0.89–2.33)	1.28	(0.76–2.15)
Dry cough	0.66	0.72	1.32	(0.81–2.17)	1.08	(0.62–1.90)
Sneeze	0.47	0.43	0.88	(0.55–1.39)	0.82	(0.48–1.38)
Stopped up nose	0.59	0.58	0.95	(0.59–1.52)	1.03	(0.61–1.75)
Runny nose	0.75	0.67	0.66	(0.39–1.11)	0.45	(0.25–0.82)
Wheeze	0.12	0.20	1.73	(0.89–3.39)	1.41	(0.63–3.15)
'Cold'	0.55	0.66	1.57	(0.98–2.52)	1.46	(0.86–2.49)
Absent from school	0.47	0.63	1.96	(1.22–3.13)	1.92	(1.13–3.25)

[a] Low exposure ≤40 ppb NO_2.
[b] High exposure >40 ppb NO_2.
[c] Confounders include asthma, early severe chest illness, allergies/hayfever, geographical area, age (<9/9+), gender.

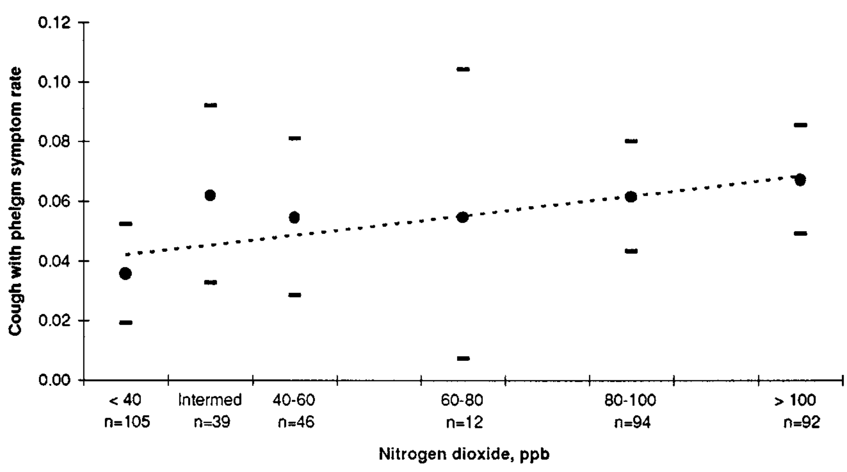

FIGURE 1 *Geometric mean symptom rates and 95% confidence intervals for cough with phlegm during the winter heating period for 388 children grouped according to estimated amount of nitrogen dioxide (NO_2) exposure at home and at school. Group means and trend (P = 0.02) estimated from mixed models allowing for correlation between children within classrooms (unadjusted for confounding)*

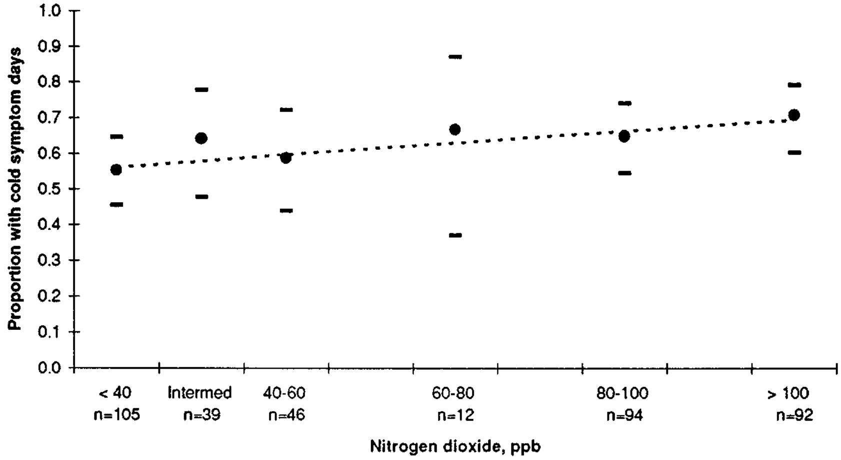

FIGURE 2 *Proportions (and 95% confidence intervals) of children with colds during the winter heating period grouped according to estimated amount of nitrogen dioxide (NO_2) exposure at home and at school (n = 388). Group means and trend (P = 0.03) estimated from Generalized (binomial) Linear Mixed Models (GLMM) allowing for correlation between children within classrooms (unadjusted for confounding)*

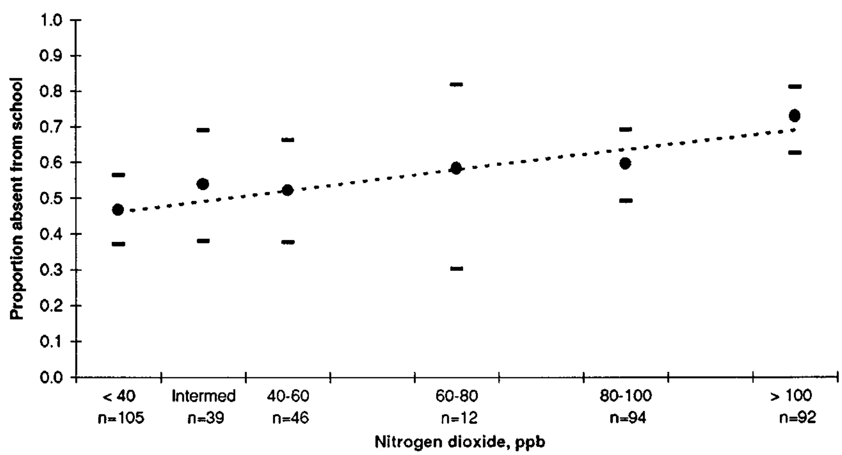

FIGURE 3 *Proportions (and 95% confidence intervals) of children absent from school for at least one day during the winter heating period grouped according to estimated amount of nitrogen dioxide (NO_2) exposure at home and at school (n = 388). Group means and trend ($P < 0.001$) estimated from Generalized (binomial) Linear Mixed Models (GLMM) allowing for correlation between children within classrooms (unadjusted for confounding)*

with phlegm was marginally significant. High exposure was also associated with a higher proportion of children who were absent from school. As well, dose-response relationships were demonstrated for these four symptoms with increasing levels of NO_2 exposure. Although absence from school is not respiratory specific, a strong dose-response was demonstrated.

The finding that highly exposed children were significantly less likely to experience runny nose may be an artefact of multiple analyses, particularly in the absence of a demonstrable dose-response relationship. This may also apply to the tests for interactions. Although gender effects, mainly involving wheezing in females, have been observed in previous studies,[25,26] differential effects of exposure were found only for dry cough in boys and for colds in girls.

In their longitudinal study of respiratory illness in children younger than 18 months, Samet *et al.*[16] found average bedroom levels of NO_2 to be mostly $<$20 ppb, but these were measures of exposure that would have averaged out the sorts of peaks that we were measuring. Also, Dijkstra *et al.*[15] found average weekly exposure estimates to be mainly $<$30 ppb, while Koo *et al.*,[14] who used passive diffusion badge monitors to measure NO_2 levels over 24 hours, found mean levels of NO_2 to be generally $<$23 ppb. These levels are comparable with the background levels found in our study. Classification of subjects by peak levels of NO_2 exposure was not possible in these other studies.

The cutpoint of 40 ppb in our study was associated with hourly peaks of the order of $\geqslant$80 ppb. These peaks were at least four times higher than the background levels of $\leqslant$20 ppb that were observed in non-gas atmospheres. Ratios of 3:1 and 4:1 peak to background levels were toxic in animal studies over a range of absolute NO_2 concentrations. Gardner,[19] Graham[20] and their co-workers examined the effect of peak exposures (4500 ppb) to NO_2, on a background of continuous low level exposure (1500 ppb). Mice were exposed to peak levels for up to 7 hours followed by bacterial exposure. When challenged by streptococcus immediately post exposure, mortality was proportional to the duration of the peak. Miller *et al.*[21] conducted a similar study using peak concentrations at an order of magnitude lower than above. Mice were exposed to a continuous baseline of 200 ppb NO_2 upon which were superimposed two one-hour peaks of 800 ppb 5 days per week. Mortality was compared with mortality in control mice, or mice that received only baseline exposure. The infectivity mortality of mice in the peak exposure regimen was significantly greater than that in either the NO_2 background exposed mice or the control mice. The ratio in the pattern of exposure could apparently influence toxicity over a wide range of absolute concentrations. Such a pattern of toxicity does not easily lend itself to setting a single air quality standard. Nevertheless, the pattern of exposures and levels of symptomatology observed in this study suggest that the World Health Organization's guideline of 210 ppb and the Australian National Health and Medical Research Council's level of concern of 300 ppb over one hour are too high.

The effects observed at the individual level are not trivial. For example, an average highly exposed child experienced 7 days of cold symptoms during the winter heating period compared to 4 days for an average child with low exposure (Table 2).

Parental knowledge about the nature of the study did not appear to influence selectively the non-response or dropout rate, which were similar between gas heated and electrically heated schools. Nevertheless, it is recognized that the study group is approximately one-third of the targeted population, and that response bias in relation to exposure was possible. The absence of significant differences between the high and low exposed children prior to gas use, at a time when NO_2 levels in all schools were similar, is reassuring.

The proportion of parental smokers (19%) in this study was low compared with the prevalence of smokers in the Australian adult population (25%).[27] This may be a function of socioeconomic status, as all the schools involved in this study were fee paying, which indicates attendance by a majority of children from middle and upper-middle class backgrounds.

Although replication studies are needed, this study raises an issue about goal levels. Exposure to NO_2 occurred in these children over periods of time greater than one hour and less than 24 hours. Measurements were taken only during periods of exposure, and were able to reflect peak and background levels that varied daily. Our findings suggest the need for a new approach to goal setting, with a timed period of, say, 6–8 hours, which would better reflect the usual exposure patterns experienced in human environments.

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