WHO GUIDELINES FOR INDOOR AIR QUALITY

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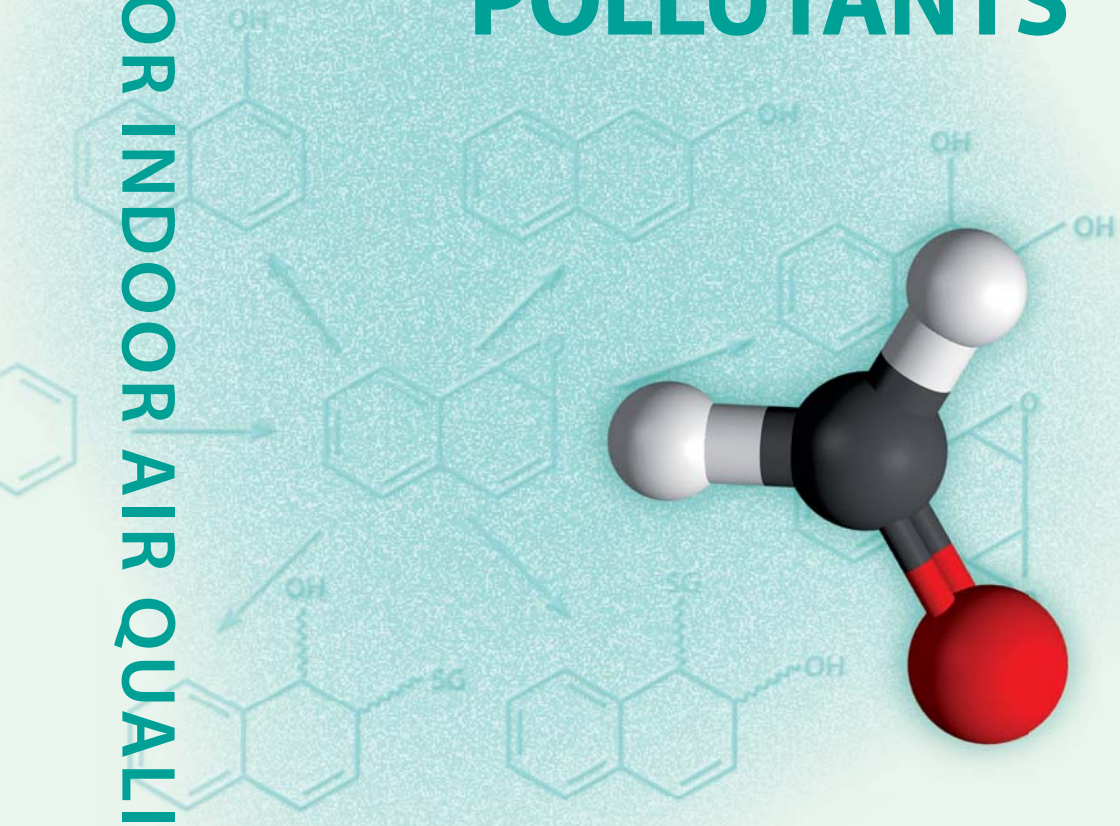
SELECTED POLLUTANTS



5. Nitrogen dioxide

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General description

There are seven oxides of nitrogen that may be found in the ambient air. Nitrous oxide (N_2O) is a greenhouse gas with significant anthropogenic sources contributing to its worldwide abundance (~ 0.3 ppm). However, nitric oxide (NO) and nitrogen dioxide (NO_2) are the two principal nitrogen oxides associated with combustion sources. Ambient concentrations of these two gases vary widely according to local sources and sinks, but can exceed a total concentration (NO + NO_2) of 500 μg/m^3 in dense urban areas. Nitrous acid (HONO) is a common pollutant in ambient and indoor environments, produced by the reaction of nitrogen dioxide with water.

Nitric oxide is oxidized in air to form nitrogen dioxide. In its liquid form, nitrogen dioxide is colourless to brown. While the boiling point of nitrogen dioxide is 21.15 °C, in normal ambient conditions its low partial pressure in the atmosphere (908 mmHg at 25 °C) prevents condensation so that it exists in the air in its gaseous form. In that form, nitrogen dioxide is volatile, reddish-brown in colour and heavier than air, and has a characteristic pungent odour perceptible from a concentration of 188 μg/m^3 (0.1 ppm). It is a strong oxidant, corrosive and poorly soluble in water *(1)*. Its molecular weight is 46.01 g/mol, melting point –11.2 °C, boiling point 21.15 °C and density 1.59 (air = 1). It reacts with water and is soluble in sulfuric and nitric acids.

Conversion factors

At 760 mmHg and 20 °C, 1 ppm = 1.914 mg/m^3 and 1 mg/m^3 = 0.523 ppm; at 25 °C, 1 ppm = 1.882 mg/m^3 and 1 mg/m^3 = 0.531 ppm.

Sources and pathways of exposure

In ambient air, the oxides of nitrogen are formed by various combinations of oxygen and nitrogen at high temperatures during the combustion process. The higher the combustion temperature, the more nitric oxide is generated. Indeed, 90–95% of the nitrogen oxides are usually emitted as nitric oxide and only 5–10% as nitrogen dioxide, although substantial variations from one source type to another have been observed. In ambient conditions, nitric oxide is rapidly oxidized in air to form nitrogen dioxide by available oxidants (such as oxygen, ozone and

VOCs) and this rapid oxidation velocity is such that it is nitrogen dioxide that is usually considered as a primary pollutant. In indoor air, however, this oxidation process is generally much slower *(2)*.

Road traffic is the principal outdoor source of nitrogen dioxide. The most important indoor sources include tobacco smoke and gas-, wood-, oil-, kerosene- and coal-burning appliances such as stoves, ovens, space and water heaters and fireplaces, particularly unflued or poorly maintained appliances. Outdoor nitrogen dioxide from natural and anthropogenic sources also influences indoor levels. Occupational exposures can be elevated in indoor spaces, including accidents with silage and in ice arenas with diesel- or propane-fuelled ice resurfacing machines *(3)* and underground parking garages *(4)*.

In ambient conditions, both outdoors and indoors, nitrogen dioxide exists in its gaseous form, and inhalation is therefore the major route of exposure at room temperature. Exceptionally, direct contact with the eyes and associated membranes may lead to eye irritation, although this is more likely to occur in industrial settings after accidental contact with relatively high gaseous nitrogen dioxide concentrations *(1)*.

Indoor levels and relationship with outdoor levels

Indoor air levels in various countries

In the INDEX report *(5)*, nitrogen dioxide concentrations were in the range of 13–62 μg/m^3 indoors, 27–36 μg/m^3 at the workplace, 24–61 μg/m^3 outdoors and 25–43 μg/m^3 for personal exposure. Maximum levels associated with the use of gas appliances (gas cooking and heating) in European homes are in the range 180–2500 μg/m^3. In studies regrouped in the THADE project *(6)*, mean indoor concentrations in Europe ranged from 10–15 μg/m^3 in Scandinavia *(7,8)* to 65 μg/m^3 in Poland *(8)*. Compared to European levels, indoor levels were similar in North America *(8)* but were higher in Asia (43–81 μg/m^3) *(8–10)*, New Mexico, USA *(11)* and Mexico *(8)*.

Levy et al. *(8)* studied nitrogen dioxide concentrations in homes in 18 cities in 15 countries, reporting two-day means ranging from 10 μg/m^3 to 81 μg/m^3 and personal exposures from 21 μg/m^3 to 97 μg/m^3. The use of a gas stove was found to be the dominant activity influencing indoor concentrations. Results showed also the importance of combustion space heaters to elevated nitrogen dioxide concentrations.

Numerous EU studies highlight the importance of key sources in characterizing indoor nitrogen dioxide levels. In an Italian population-based study, the highest weekly indoor concentrations were measured in a rural area of the Po Delta. The weekly mean indoor concentration in the kitchen during winter was higher than that in summer, being 62 μg/m^3 and 38 μg/m^3, respectively. The study also found that the presence of a gas-fired heating furnace was the major factor in the elevated nitrogen dioxide concentrations *(12)*. In a Spanish study of 340 dwell-

ings carried out between 1996 and 1999, average annual indoor concentrations of nitrogen dioxide did not vary significantly, ranging from 12.5 to 14.7 μg/m^3. Respective outdoor air concentrations were slightly higher in 1996 and 1998 and slightly lower in 1997 and 1999; typical indoor : outdoor ratios were close to 1. The principal indoor sources of nitrogen dioxide in Spanish homes were the use of gas cookers, the absence of an extractor fan when cooking, the absence of central heating, and cigarette smoking *(13)*. Consistent risk factors were identified when these data from Barcelona were compared with cohort data from Ashford, Kent (United Kingdom) and Menorca (Spain). In the United Kingdom, studies showed indoor concentrations of nitrogen dioxide in homes without gas stoves ranging from 13 to 40 μg/m^3 and in the presence of gas stoves from 25 to 70 μg/m^3 *(14)*.

Nitrogen dioxide concentrations in indoor air in different countries, the microenvironments and the different fuel sources are summarized in Table 5.1 (see page 268).

Factors influencing nitrogen dioxide levels indoors

Box 5.1 summarizes some of the key factors that influence indoor nitrogen dioxide levels and likely explain much of the variation reported in Table 5.1. Indoor levels of nitrogen dioxide are a function of both indoor and outdoor sources. Thus, high outdoor levels originating from local traffic or other combustion sources influence indoor levels. Annual mean concentrations in urban areas throughout the world are generally in the range of 20–90 μg/m^3 *(15)*. In the European Community Respiratory Health Survey (ECRHS II) covering 21 European cities, annual ambient nitrogen dioxide concentrations ranged from 4.9 μg/m^3 in Reykjavik to 72 μg/m^3 in Turin *(16)*. The maximum hourly mean value may be several times higher than the annual mean. For example, a range of 179–688 μg/m^3 nitrogen dioxide has been reported inside a car in a road tunnel during the rush hour *(15)*.

The distance of buildings from roadways appears to have an impact on indoor nitrogen dioxide levels *(17,18)*. Levels in school classrooms have been found to be significantly correlated with traffic density and distance of the school from the roadway *(19)*.

The air rate exchange between indoors and outdoors affects nitrogen dioxide levels in buildings. Indoor levels vary widely depending on the presence of indoor sources, air mixing within and between rooms, the characteristics and furnishing of buildings, and reactive decay on interior surfaces. Further, it has been shown that car exhausts containing nitrogen dioxide may enter a house from an attached garage *(20)*.

In the absence of indoor nitrogen dioxide sources, indoor levels will be lower than outdoor levels. Under normal ventilation conditions, the indoor : outdoor ratio has been found to vary from 0.88 to 1 *(21)*. This is attributable to the re-

Box 5.1. Factors that influence indoor concentrations of nitrogen dioxide

Indoor sources

Fuel-burning stoves (wood, kerosene, natural gas, propane, etc.)
Fuel-burning heating systems (wood, oil, natural gas, etc.)
Tobacco use

Source characteristics

Flued/unflued sources
Presence of pilot lights

Outdoor sources (via infiltration)

Mobile sources (petrol- and diesel-powered vehicles)
Stationary sources (industrial combustion)

Resident behaviour

Stove usage (for fuel-burning appliances)
Use of heating equipment (including cooking stoves)

Dwelling and indoor environment characteristics

Dwelling size (where there are indoor sources)
Air exchange rates
Distance to roadway
Surface characteristics
Indoor humidity

moval of nitrogen dioxide by the building envelope and its reactions with interior surfaces and furnishing *(22)*. However, in the presence of indoor sources, especially unvented combustion appliances, indoor levels may exceed those found outdoors *(23)* with an increase in the indoor : outdoor ratio from 0.7 without an indoor source to 1.2 in the presence of an indoor source *(3,24,25)*. These ratios, however, reflect average levels over several days of measurement and do not reflect the more extreme indoor/outdoor differences that one would expect to see over shorter periods of time – for example, when a gas appliance is being used inside a home.

The presence and use of indoor sources are the primary determinants of indoor nitrogen dioxide levels within populations. In an inner-city population in the United States, mean nitrogen dioxide concentrations were higher in homes with a gas stove (33.1 ppb or 63.3 $\mu g/m^3$) than in those without a gas stove (16.8 ppb or 32.1 $\mu g/m^3$) *(26)*. In this study, indoor levels were also associated with the presence of a gas heater and the use of a space heater or oven for supplementary heating.

The average nitrogen dioxide concentration over a period of several days may exceed 150 $\mu g/m^3$ when unvented gas stoves are used *(27)*. On the other hand, wood-burning appliances were not related to elevated nitrogen dioxide concentrations in a Canadian study carried out in 49 houses *(28)*. While most studies

of indoor air pollutant exposures from biomass burning in developing countries have focused on airborne particulate matter, nitrogen dioxide levels can also be elevated. In a study in Ethiopia where wood, crop residues and animal dung were the main household fuels, the mean 24-hour concentration of nitrogen dioxide was 97 μg/m^3 *(29)*. A study in rural, urban and roadside locations in Agra, India showed the dominance of outdoor sources (principally diesel generators and traffic) on elevated indoor nitrogen dioxide concentrations (indoors 255 ± 146 ppb; outdoors 460 ± 225 ppb) *(30)*.

Indoor levels are typically higher in winter than in summer, probably owing to increased use of heating, lower ventilation rates and higher outdoor concentrations *(11,14,31,32)*. In the recently published ECRHS II study carried out in 21 European cities, concentrations in winter exceeded summer values with an average winter : summer ratio of 1.50 *(16)*.

There are limited data on nitrogen dioxide peaks. However, it has been shown that, in homes, peak concentrations are typically related to the use of combustion appliances for cooking and heating *(32–35)*. In particular, occurrences of peaks are strongly associated with the use of gas and solid fuel stoves, the highest nitrogen dioxide concentrations coinciding with the time of meal preparation *(36)*. In a study of Australian homes, the mean peak-to-average nitrogen dioxide ratio was 2.9 (1.2–4.6) for homes without gas cookers and 7.8 (2.6–13.0) for those with gas cookers *(37)*. A modelling study of indoor nitrogen dioxide exposures in the United Kingdom concluded that those regularly using gas for cooking would experience 1-hour mean exposures above 287 μg/m^3 (150 ppb) for at least 1 hour on every day of the year *(38)*. Reported maximum measured nitrogen dioxide levels associated with the use of gas appliances in homes are in the range 150–2055 μg/m^3 over 1 hour, with peaks of 400–3808 μg/m^3 for 1 minute *(27,34)*.

In addition to the direct release of nitrogen oxides, indoor combustion sources emit various co-pollutants including ultrafine particles, which are also produced during cooking *(36)*. Secondary reactions, such as the production of nitrous acid from surface chemistry involving nitrogen dioxide, can contribute to indoor pollutant concentrations that directly affect health *(39,40)*. The role of these co-pollutants in the health effects attributed to nitrogen dioxide in field studies is unknown, but abatement measures for nitrogen dioxide, such as improved ventilation, will be beneficial in reducing co-exposures also.

High nitrogen dioxide concentrations are also associated with the use of candles and mosquito coils. In chamber (18 m^3) tests, maximum nitrogen dioxide concentrations up to 92 μg/m^3 were observed during incense burning *(41)*. High values of nitrogen dioxide up to 7530 μg/m^3 were also reported in enclosed ice arenas with inadequate ventilation from the exhaust emissions of propane- and petrol-fuelled ice resurfacing machines *(42,43)*. The link between direct source exposure and high nitrogen dioxide levels was noted in a small study of unvented natural gas fireplaces (mean 688.7 μg/m^3; n = 2) *(33)*.

Indoor concentrations of nitrogen dioxide are also subject to geographical, seasonal and diurnal variations. Differences in the indoor concentrations in various countries are mainly attributable to differences in the type of fuel used for cooking and heating and the rate of fuel consumption. While few studies have included repeated measurements of indoor nitrogen dioxide levels, it is known that within-home variability can be significant owing to the various contributing factors discussed above *(44)*.

Seasonal variability can be significant, owing to variations in source use (e.g. heaters and stoves) and seasonal fluctuations in air exchange rates. This variability results typically in higher indoor concentrations during winter months *(31,45,46)*. This variability, and its principal determinants, should be considered when extrapolating from exposure estimates determined using daily or weekly measurements to estimates of annual exposures. Since few (if any) studies have directly measured annual averages of indoor nitrogen dioxide concentrations, periodic measurements across seasons would be needed to construct representative estimates of long-term exposure.

Kinetics and metabolism – effects observed in experimental studies

In vitro studies

As nitrogen dioxide is a free radical, it has the potential to deplete tissue antioxidant defences and, as a consequence, cause injury and inflammation as shown in a variety of in vitro test systems. Exposure of human blood plasma to 26 230 $\mu g/m^3$ (13.95 ppm) nitrogen dioxide resulted in a rapid loss of ascorbic acid, uric acid and protein thiol groups, in addition to lipid peroxidation and a depletion of alpha-tocopherol (vitamin E) *(47)*.

In another study, exposure to nitrogen dioxide over a lower concentration range (94–1880 $\mu g/m^3$; 0.05–1.0 ppm) resulted in the antioxidant defences, uric acid and ascorbic acid being depleted in human bronchoalveolar lavage (BAL) fluid *(48)*. More recently, Olker et al. *(49)* have shown that superoxide radical release is significantly impaired from BAL cells isolated from rats exposed to nitrogen dioxide (18 800 $\mu g/m^3$; 10 ppm) for 1, 3 or 20 days. This was explained by decreased production as a result of an inhibition of NADPH oxidase and complex III of the respiratory chain, and to a lesser extent increased scavenging brought about by enhanced glutathione peroxidase and CuZn-superoxide dismutase mRNA expression and enzyme activities. Evidence for the role of oxidative stress in the effects of nitrogen dioxide on respiratory virus-induced injury comes from a study that found that pre-treatment of cultured primary human nasal epithelial cells and cells of the BEAS-2B line with the antioxidant *N*-acetylcysteine inhibited the production of IL-8 following exposure to 3160 $\mu g/m^3$ (2 ppm) nitrogen dioxide for three hours in combination with human rhinovirus type 16 (RV16) *(50)*.

Cell culture systems have also been used to describe nitrogen-dioxide-mediated cell injury and inflammation. One system exposed cultured human bronchial epithelial cells to 7520 and 15 040 μg/m^3 (4.0 and 8.0 ppm) nitrogen dioxide and elicited cell membrane damage and increased membrane permeability *(51)*. It should be remembered that confluent airway epithelial cell monolayers in vitro are not fully differentiated and posses a markedly decreased level of resistance to pollutants when compared to the epithelium in the intact human. However, in a more physiologically relevant system, nitrogen dioxide (200 and 800 μg/m^3; 0.1 and 0.43 ppm) has also been shown to trigger inflammation in cultured human nasal mucosa explants, using histamine release into the culture medium as a marker of the inflammatory response *(52)*. The early pro-inflammatory responses following exposure to a brief high concentration of nitrogen dioxide – up to a maximum of 84 600 μg/m^3 (45 ppm) over 50 minutes – have also been assessed using normal human bronchial epithelial (NHBE) cells as an in vitro model of inhalation injury *(53)*. While immunofluorescence studies confirmed oxidant-induced formation of 3-nitrotyrosine, the nitrogen-dioxide-exposed cells exhibited marked increases in the levels of nitrite (used as an index of nitric oxide), IL-8, IL-1β and TNF-α. Further, to simulate a pre-existing "inflammatory" condition of the bronchial epithelium, such as would exist in asthma and other hyperreactive airway diseases, cells were pre-treated with various pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β and IL-8) for 24 hours prior to exposing them to nitrogen dioxide. The combination of cytokine treatment and nitrogen dioxide exposure consistently enhanced the generation of nitric oxide and IL-8. More recently, further findings have been published on the early changes in NHBE cells on exposure to a brief high dose (84 600 μg/m^3; 45 ppm) of nitrogen dioxide, focusing on the nature and time-course of nitrogen-dioxide-mediated cell death and, more generally, on the cellular mechanisms by which the various pro-inflammatory mediators affect the target cells *(54)*. Cells were found to undergo apoptotic cell death during the early post-nitrogen-dioxide period, independent of any significant increase in caspase-3 activity, while necrotic cell death was more prevalent at later time intervals. Exposed cells also exhibited increased expression of heme oxygenase-1 (HO-1), a redox-sensitive stress protein, at 24 hours and increased adhesion to neutrophils, which in turn resulted in an increased NHBE cell death. Earlier reports of an involvement of nitric oxide *(53)* were supported by the significant decrease in cell death and neutrophil adhesion in the presence of nitric oxide synthase inhibitors (L-NAME and 3-aminoguanidine) *(54)*.

Effects on experimental animals

Nitrogen dioxide per se, but not specifically in relation to indoor sources/exposure patterns, has been shown to exert a range of biological effects on experimental animals, including changes in lung metabolism, structure, function, inflam-

mation and host defence against infectious pulmonary disease. Such effects vary widely, however, depending on the species and strain exposed, the concentration and duration applied, and the age and sex of the animals *(55)*.

In extrapolating the aforementioned data to humans, it is the anatomical and physiological differences between animals and humans that represent a particular challenge. For example, we have known for some time from mathematical modelling that the distribution of nitrogen dioxide deposition within the respiratory tract of rats, guinea-pigs, rabbits and humans appears to be similar *(56–58)*. More recently however, Tsujino et al. *(59)*, using mathematical airway models of rats, dogs and humans, demonstrated that interspecies variations in anatomy and respiratory patterns do cause significant differences in the concentration of nitrogen dioxide in the airways and alveoli. Despite some limitations, owing to many simplifications and assumptions necessary to construct the airway model and carry out calculations, intra-airway nitrogen dioxide concentrations were higher in the upper and lower airways of humans compared with rats and dogs, while those in the alveolar regions were lowest in humans.

Pulmonary metabolism

The majority of biochemical studies show effects only after acute or subchronic exposure to high levels of nitrogen dioxide exceeding 3160 μg/m^3 (2 ppm) *(60–62)*. A notable exception is the effect on lung lipid metabolism. Continuous exposure of rats to concentrations as low as 752 μg/m^3 (0.4 ppm) for 18 months increased lipid peroxidation when thiobarbituric acid reactants were used as an indicator, while lipid peroxidation was raised by 75 μg/m^3 (0.04 ppm) for 9 months when ethane exhalation was the indicator *(63,64)*. Effects on both lipid and antioxidant metabolism showed a response pattern that depends on both concentration and duration of exposure *(65)*. Frequently observed features at higher nitrogen dioxide levels include the induction of lung oedema, an increase in antioxidant metabolism, an increase in lung enzymes associated with cell injury, and changes in lung lipids. On investigating the basis of oxidative stress elicited in rats exposed to 18 880 μg/m^3 (10 ppm) nitrogen dioxide for 3 and 20 days (inducing acute and chronic lung injury, respectively), Hochscheid et al. *(66)* reported an imbalance of glutathione status (by analysing the activity and mRNA expression of a host of enzymes involved in glutathione metabolism) in type II pneumocytes following both types of lung injury.

In relation to nitrogen-dioxide-induced oxidative stress and perturbations in antioxidant metabolism, a potential protective role that antioxidant status may play in influencing the lung response to pollutant exposure has been explored *(67)*. The effects of a low-selenium diet (1.3 μg/day) with or without selenium supplementation in rats exposed to either acute (62 000 μg/m^3 (50 ppm) for 30 minutes), intermittent subacute (5 ppm, 6 hours/day for 5 days) or intermittent long-term nitrogen dioxide (1 or 10 ppm, 6 hours/day, 5 days/week for 28 days)

on a host of markers were examined and the majority of these (particularly those indicating increased permeability of the lung epithelial barrier) indicated the protective role of normal selenium status.

Although still not fully understood, alterations in pulmonary metabolism may be early signs of cell lesions, which become manifest only at higher concentrations or upon longer exposure *(60–62,68,69)*.

Pulmonary structure

In the tracheobronchial and alveolar regions, nitrogen dioxide at concentrations down to 640 μg/m^3 (0.34 ppm) results in replacement of the type I alveolar epithelial and ciliated epithelial cells with the more oxidant-resistant type II and nonciliated bronchiolar (Clara) cells, respectively. Furthermore, the replaced cells exhibit alterations of their cytoplasm and hypertrophy after short exposure (10 days) to concentrations of nitrogen dioxide above 940 μg/m^3 (0.50 ppm), the significance of which is not known (*60–62,69)*. We do, however, appreciate that both the exposure regimen used and the time of exposure are important. In a subchronic study of lung lesions in rats, Rombout et al. *(70)* showed that the concentration (C) of inhaled nitrogen dioxide had more influence on epithelial metaplasia than exposure duration (time, T) when C × T was constant, and that the effect of C was greater with intermittent exposure than with continuous exposure. Other experiments have addressed the temporal pattern of nitrogen dioxide effects and found them to be complex *(60)*. For example, over a 7-day period, a wave of epithelial hyperplasia occurs, peaking by about day 2 *(71)*. Rombout et al. *(70)* showed that even 2 months after a 1-month exposure ceased, some nitrogen-dioxide-induced interstitial changes were still present.

Long-term exposure to nitrogen dioxide leads to emphysema-like structural changes in animals, in addition to thickening of the alveolar capillary membrane, loss of ciliated epithelium and increases in lung collagen. Such changes have been observed in mice, rats, dogs and monkeys (*60–62,68)*. In 1993, the USEPA reviewed 23 research reports on nitrogen dioxide exposure and emphysema to determine whether the effects reported met the US National Heart, Lung, and Blood Institute definition for human emphysema *(72)*. This can be important because the animal studies were of interest for the purposes of extrapolation to humans, whether or not the more rigorous definition of human emphysema (which includes destruction of alveolar walls) is met. Many of the reports contained insufficient detail to permit an independent judgement as to whether "human-type" emphysema had occurred. Nevertheless, three studies reported convincing evidence of human-type emphysema following exposure to very high nitrogen dioxide levels relative to ambient concentrations: Haydon et al. *(73)* exposed rabbits to 15 040–22 600 μg/m^3 (8–12 ppm) for 3–4 months; Freeman et al. *(74)* exposed rats to 37 000 (reduced to 28 200 or 18 800) μg/m^3 (20, reduced to 15 or 10 ppm) for up to 33 months; and Hyde et al. *(75)* exposed dogs for 5½ years to a

mixture containing 1210 μg/m^3 (0.64 ppm) nitrogen dioxide and 310 μg/m^3 (0.25 ppm) nitric oxide, respectively. These animals exhibited several decrements in pulmonary function, which continued to deteriorate compared to controls during a 2½-year post-exposure period in clean air. After this post-exposure period, lung morphometry studies showed changes analogous to human centrilobular emphysema.

Studies undertaken to localize collagen deposition within the lung have exposed ferrets to 940 or 18 800 μg/m^3 (0.5 or 10 ppm) of nitrogen dioxide for 4 hours a day for 8 or 15 weeks. Increased lung collagen deposition was identified within the respiratory bronchiolar submucosa, although this was only significant in the higher-dose group *(76)*. The onset of emphysema-like changes, together with the major features characteristic for human chronic obstructive pulmonary disease (COPD), have also been reported in another study in which mice were exposed to 31 160 μg/m^3 (20 ppm) nitrogen dioxide for 14 hours a day for up to 25 days *(77)*. The main findings were progressive airway inflammation with a marked influx of neutrophils and macrophages, goblet cell hyperplasia indicative of increased mucus hypersecretion in the central airways, progressive airflow obstruction and focal parenchymal inflammation associated with airspace enlargement. Exposure of rats to 18 880 μg/m^3 (10 ppm) nitrogen dioxide for 23 hours per day for 3, 7 or 21 days, or 21 days followed by 28 days in room air, resulted in increased alveolar septal cell turnover, indicated by an 8-fold increase in alveolar septal cell apoptosis at day 3 and a 14-fold increase in proliferation *(78)*. These changes led to accelerated lung growth, characterized by an imbalance in the relative composition of the extracellular matrix, but failed to induce emphysema. Indeed, although airspace enlargement was evident, nitrogen dioxide resulted in an increase in the total surface area and absolute volume of alveolar walls comprising all compartments.

Pulmonary function

Exposure to nitrogen dioxide at concentrations of 376–18 800 μg/m^3 (0.2–10 ppm) has been shown to affect pulmonary function in several animal species (rats, mice, guinea-pigs and ferrets). The extent of an effect may be influenced by the mode of exposure, in that compared to continuous exposure (376 μg/m^3; 0.2 ppm) alone, a greater reduction in end-expiratory volume, vital capacity and respiratory system compliance was shown in mice chronically exposed to 1-hour spikes (twice a day) of 1504 μg/m^3 (0.8 ppm) of nitrogen dioxide superimposed on the baseline exposure *(79)*. Adult rats exposed for 6 weeks to 940 μg/m^3 (0.5 ppm) nitrogen dioxide and daily 1-hour spikes of 2820 μg/m^3 (1.5 ppm) experienced reduced lung compliance that returned to normal 3 weeks post-exposure *(80)*. An increase in lung volume and compliance was seen (at 3 weeks but not at 6 weeks) in neonatal rats exposed to an identical regimen *(80)*. A chronic (78-week) exposure study assessed a number of pulmonary function parameters in

rats exposed to nitrogen dioxide (940 μg/m^3 (0.5 ppm) background with a daily peak rising to 2820 μg/m^3 (1.5 ppm)). No changes in compliance, lung volume or diffusion capacity of carbon monoxide were seen, while a decrease in the delta forced expiratory flow at 25% of forced vital capacity disappeared soon after the end of exposure *(81)*. In guinea-pigs exposed to 112.8, 940 or 1880 μg/m^3 (0.06, 0.5 or 1.0 ppm) nitrogen dioxide for 6 or 12 weeks, significant effects were limited to an increase in pulmonary specific airway resistance in 13% (2 of 15) of animals following the 12-week 1.0-ppm exposure regimen *(82)*. The effect of exposure to either 940 or 18 800 μg/m^3 (0.5 or 10 ppm) nitrogen dioxide on tracer particle clearance from the airways of ferrets during postnatal respiratory tract development has also been examined. Thoracic clearance was reduced in both exposure groups, but was not significantly different in the 940-μg/m^3 (0.5-ppm) group compared to that of the control animals exposed to clean air *(76)*.

Airway inflammation and responsiveness

The effects of short-term (24-hour) exposure to nitrogen dioxide on airway eosinophilic inflammation and bronchial hyperreactivity have been examined using a standard murine model of antigen-modified broncho-constriction and airway inflammation *(83)*. BALB/c mice were sensitized to ovalbumin and exposed to 3760 μg/m^3 (2.0 ppm) nitrogen dioxide prior to being challenged with aerosolized ovalbumin on days 13 and 14. Nitrogen dioxide was found to enhance epithelial damage, reduce mucin expression and increase baseline smooth muscle tone. Although a modest increase in airway neutrophilia was detected, exposure was not associated with airway eosinophilia or with an increase in bronchial hyperresponsiveness. In contrast, Poynter et al. *(84)* reported no changes in the inflammatory response in C57BL/6 mice immunized and challenged with ovalbumin before exposure to 3 days of 9400 μg/m^3 (5 ppm) nitrogen dioxide. A 5-day inhalation of 31 000 μg/m^3 (25 ppm) nitrogen dioxide was, however, found to prolong ovalbumin-induced inflammation and airway hyperresponsiveness. Findings included acute damage associated with inflammation and lesions in the alveolar duct region and an influx of macrophages and neutrophils into the lavageable air spaces. Moreover, 20 days after cessation of the inhalation regimen, eosinophilic and neutrophilic inflammation, pulmonary lesions and airway hyperresponsiveness were still present.

A hypothesis that nitrogen dioxide acts as an effective inhaled adjuvant that accentuates the adaptive immune response to otherwise innocuous antigens prompted a study in which mice were exposed first to 18 880 μg/m^3 (10 ppm) nitrogen dioxide and then to aerosolized 1% ovalbumin *(85)*. Mice were subjected to the same sensitization regimen one week after and challenged with 1% ovalbumin alone an additional week later. Following the final challenge with ovalbumin, mice developed eosinophilic inflammation, mucus cell metaplasia, airway hyperresponsiveness and antigen-specific IgE and IgG1, and Th2-type cytokine

responses. The authors likened these changes to the phenotypic alterations in allergic asthma and those elicited following ovalbumin challenge in antigen-sensitized mice.

The inflammatory response to nitrogen dioxide, with particular focus on the activation state of alveolar macrophages, has been studied in a rat inhalation model using continuous exposure to 18 800 μg/m^3 (10 ppm) for 1, 3 and 20 days *(86)*. Whereas the number of inflammatory cells and total protein concentration in BAL were increased, TNF-α was markedly reduced with increasing exposure time. In contrast, IL-10, IL-6 and suppressor of cytokine signalling-3 protein were elevated. Furthermore, in vitro lipopolysaccharide stimulation of BAL cells revealed reduced capability to produce TNF-α, IL-1 β and nitric oxide, but showed markedly increased transcription and protein release for IL-10. In addition, elevated levels of IL-6, scavenger receptor B and suppressor of cytokine signalling-3 mRNA were detected in BAL cells from exposed animals. Analyses of highly purified alveolar macrophages indicated that changes in the activation state of these cells were most likely responsible for the observed effects.

To increase our understanding of the contribution of nitrogen dioxide to the development of COPD, Brandsma et al. *(87)* studied the effects of combined exposure to nitrogen dioxide and cigarette smoke on pulmonary inflammation and emphysema. Mice were exposed to either 31 160 μg/m^3 (20 ppm) nitrogen dioxide for 17 hours a day, 24 puffs of cigarette smoke twice a day or both, 5 days a week for 4 weeks. Cigarette smoke exposure increased eosinophil numbers and levels of TNF-*α*, KC (mouse IL-8), monocyte chemoattractant protein (MCP)-1, and IL-6. Nitrogen dioxide exposure increased goblet cells, eosinophils and the levels of IL-6, while it reduced the levels of IL-10. Four weeks of nitrogen dioxide, cigarette smoke or both was not sufficient to induce significant emphysema, nor did it lead to lower numbers of lymphocytes, neutrophils or macrophages in lung tissue. Instead, nitrogen dioxide exposure dampened the cigarette smoke-induced increases in the inflammatory cytokines TNF-*α*, KC and MCP-1. The authors suggested that these attenuating effects may be due to modulating effects of nitrogen dioxide on cytokine production by macrophages and epithelial cells. Clearly, cigarette smoke contains a range of radical species, including nitrogen dioxide, and these data may simply reflect the induction of similar pathways by both challenges.

Host defence

Several types of animal study have indicated that nitrogen dioxide increases susceptibility to respiratory infections *(60,61,88–90)*. An extensive set of data was collected using the infectivity model, which measures the total antibacterial defences of the lungs of mice. For long-term exposures, the lowest concentration tested that increased mortality when challenged with *Klebsiella pneumoniae* was 940 μg/m^3 (0.5 ppm) for 3 months of exposure *(91)*. After a 3-hour exposure, the

lowest concentration tested that affected resistance to *Streptococcus pneumoniae* was 3760 μg/m^3 (2 ppm) *(92)*. Continuous exposure to concentrations ranging from 52 640 to 940 μg/m^3 (from 28 to 0.5 ppm) resulted in linear, concentration-related increases in mortality due to pulmonary infection *(93)*. Other studies have shown that peak and patterns of nitrogen dioxide exposure are important in determining response *(60,79,94)*. For example, Miller et al. *(79)* found that infectivity, mortality and pulmonary function deficits in mice were significantly greater following a spiked exposure regimen (up to 52 weeks of continuous baseline 376 μg/m^3 (0.2 ppm) plus spikes of 1504 μg/m^3 (0.8 ppm) compared to the baseline exposure alone). In mice exposed to nitrogen dioxide at 8460 μg/m^3 (4.5 ppm) for 1, 3½ or 7 hours and challenged with *Streptococcus* sp. either immediately or 18 hours after exposure, the mortality rate was directly related to the length of peak exposure when the streptococcal challenges were immediately after nitrogen dioxide exposure but this was not the case when the challenge was delayed for 18 hours *(94)*. In summary, the body of work shows that the effects of nitrogen dioxide are due more to concentration than to duration of exposure or to total dose (expressed as C × T), that differences in species sensitivity exist, that the lowest effective concentration of nitrogen dioxide also depends on the microbe used in the test, and that low levels only cause effects after repeated exposures *(60–62,68)*. The extrapolation of these findings to humans cannot be made directly, because most of the studies used pneumonia-induced mortality as an end-point. However, the infectivity model reflects alterations in the defence mechanisms of mice that are shared by humans. Nevertheless, the quantitative relationship between effective nitrogen dioxide levels in animals and in humans is unknown. Although numerous studies provide evidence of the effects on the systemic humoral and cell-mediated immune systems, these studies are difficult to interpret *(60,61)*.

In mice, an exposure of 9400 μg/m^3 (5 ppm) nitrogen dioxide (following the bacterial challenge) was required to impair the intrapulmonary killing of *Staphylococcus aureus (90)*. The same effect, however, was found at 3100 μg/m^3 (2.5 ppm) or less in lungs immunosuppressed with corticosteroids, while the adverse effect of the pollutant was only evident at 18 800 μg/m^3 (10 ppm) when exposure preceded the bacterial challenge *(90)*.

The association between exposure to common air pollutants, including nitrogen dioxide, and altered host immunity to respiratory viral infections has recently been reviewed *(95)*. Two studies by Rose et al. *(88,89)* exposed mice to nitrogen dioxide at 9400 μg/m^3 (5 ppm) for six hours per day for two days prior to infection with murine cytomegalovirus, followed by another four days of nitrogen dioxide. The mice exposed to nitrogen dioxide not only required 100-fold less virus to become infected (possibly due to reduced phagocytosis and macrophage destruction of the virus in the pollutant-exposed mice) but were more likely to be re-infected with murine cytomegalovirus, suggesting that exposure

can adversely affect the development of virus-specific immunity. Enhanced susceptibility to infection was not found after exposure to 3100 or 1800 μg/m^3 (2.5 or 1 ppm) nitrogen dioxide. In another study using mice and the Sendai virus, while exposure to 9400 μg/m^3 (5 ppm) nitrogen dioxide for four hours per day did not alter infection it did enhance lung damage, which was suggested to have been caused by increased proliferation of the virus *(90)*.

Mutagenic/genotoxic/carcinogenic effects

There are no reports among the limited number of carcinogenicity studies that nitrogen dioxide causes malignant tumours or teratogenesis *(60,61,96,97)*. High (11 280–28 200 μg/m^3; 6–15 ppm) concentrations of nitrogen dioxide have been shown to be mutagenic in bacterial (*S. typhimurium*) test systems *(98)*. In vitro genotoxicity studies have reported chromosomal aberrations, sister chromatid exchanges or DNA single strand breaks at concentrations ranging from as high as 31 160 μg/m^3 (20 ppm) to as low as slightly over 1800 μg/m^3 (1 ppm) but not 940 μg/m^3 (0.5 ppm) *(99–101)*. Genotoxicity studies in vivo have produced mixed results. While lung cells of rats exposed to nitrogen dioxide for three hours exhibited increased mutation to ouabain resistance at 28 200 μg/m^3 (15 ppm) and increased chromosome aberrations at 15 040 μg/m^3 (8 ppm) *(102)*, no genotoxic effects were reported in alveolar macrophages of rats exposed to 2256 μg/m^3 (1.2 ppm) for three days *(103)*, in bone marrow after inhalation by mice of 31 160 μg/m^3 (20 ppm) for 23 hours *(104)* and in spermatocytes or lymphocytes of mice following a six-hour exposure to 180–18 000 μg/m^3 (0.1–10 ppm) *(105)*. Numerous studies of the interaction of nitrogen dioxide with other air pollutants, predominantly ozone, show that the effects are due to ozone alone, are additive or are synergistic, depending on the end-point and exposure regimen *(60)*.

Reproductive effects

A recent study has examined effects in the rat of fetal exposure to diesel-engine exhaust containing nitrogen dioxide at 1504 or 188 μg/m^3 (0.80 or 0.10 ppm) with or without particulate matter (1.71 or 0.17 mg/m^3) on testicular cell numbers and daily sperm production in adulthood *(106)*. The mature rats that were exposed to diesel exhaust from gestational day 7 to delivery showed a decrease in the daily production of sperm due to an insufficient number of Sertoli cells. All exhaust-exposed groups showed almost the same reactions to the inhalation, indicating that the gaseous phase must have included the responsible toxicants; these were not identified, although nitrogen dioxide would be a major constituent.

Experimental studies – summary

Experimental animal work on the health effects, and mechanisms thereof, of nitrogen dioxide has not focused on indoor sources or exposure patterns

of the pollutant (other, of course, than to have conducted all studies in an indoor environment). As such, in addition to newly published work, the studies reviewed in this section include those described in WHO's latest guidelines for ambient nitrogen dioxide *(15)*. Acute exposures (hours) to low (75–1880 μg/m^3; 0.04–1.0 ppm) levels of nitrogen dioxide have rarely been observed to cause effects in animals. Subchronic and chronic exposures (weeks to months) to low levels, however, cause a variety of effects, including alterations to lung metabolism, structure and function, inflammation and increased susceptibility to pulmonary infections. Emphysema-like changes (destruction of alveolar walls and airspace enlargement), features characteristic of human COPD (increased mucus production and progressive airway obstruction), generation of an atopic immune response and airway hyperresponsiveness have been reported only at high (15 040–47 000 μg/m^3; 8–25 ppm) nitrogen dioxide concentrations. It is apparent from both in vitro and animal toxicology studies which toxic effects of nitrogen dioxide *might* occur in humans. Nevertheless, owing to (*a*) the frequent use of extremely high exposure concentrations in experimental studies, (*b*) the inherent differences between mammalian species and (*c*) the dearth of information available on tissue response of different species to a given dose of nitrogen dioxide, it is difficult to extrapolate quantitatively, with any degree of confidence, the effects that are *actually* caused by a specific inhaled dose or concentration.

An important point, worthy of consideration, is the possible interaction between nitrogen dioxide and other indoor pollutants. It is increasingly acknowledged by indoor environmental scientists that it is the reactions between primary pollutants, creating secondary pollutants indoors, that are probably responsible for adverse health effects.

Health effects

A plethora of outdoor studies have examined the health effects of exposure to outdoor nitrogen dioxide. While there are concerns that some of the associations reported for health effects and outdoor nitrogen dioxide may be explained by co-pollutants, extensive reviews have concluded that respiratory health is associated with nitrogen dioxide exposure, independently of these other exposures *(15,107)*.

Outdoor nitrogen dioxide is increasingly being implicated in a wide range of disorders. For example, increased risk of otitis media *(108)*, eczema *(109)* ear/nose/throat infections and sensitization to food allergens *(110)* in children, as well as increased blood coagulability after periods of elevated ambient exposure in adults *(111)* have recently been reported. There is also an increasing interest in the role of outdoor pollution with reproductive outcomes *(112)*. A full review of these is beyond the scope of this report. This section will:

- briefly summarize conclusions from earlier WHO reports on the evidence for health effects based on controlled human exposure studies;

- review the epidemiological evidence for health effects of exposure to indoor nitrogen dioxide where nitrogen dioxide has been directly measured; and
- review the epidemiological evidence for health effects of exposure to gas appliances in the home – a proxy marker for high exposure to indoor nitrogen dioxide.

Controlled human clinical studies

Studies in which exposure to nitrogen dioxide has been carefully controlled in small numbers of selected participants have been reviewed in several previous publications *(15,62,107)*. These studies have examined symptoms, changes in pulmonary function and changes in airway reactivity in healthy volunteers and in those with pre-existing lung disease. Some studies have included bronchoalveolar lavage following exposure and have provided information on the inflammatory changes that may occur.

There are some inconsistencies in the results of these studies but studies on healthy volunteers can be summarized as follows.

- Measurable change in lung resistance, total airway resistance and bronchial responsiveness to acetylcholine and methacholine in healthy volunteers has been seen at exposures in excess of 1880 μg/m^3, although in one study exposures well in excess of this (7520 μg/m^3 for 75 minutes) failed to show any change *(113)*.
- A study in which nitrogen dioxide exposure was followed by bronchoalveolar lavage with assessment of cell profile in lavage fluid and in blood suggested that high exposure (up to 2821 μg/m^3 for three hours) is associated with mild airway inflammation, changes in white blood cells and increased susceptibility of airway epithelial cells to injury from respiratory virus (as assessed in vitro) *(114)*. Two studies (one at 2821 μg/m^3, the other at 7524 μg/m^3 and both for 20 minutes on 6 occasions) found decreased alveolar macrophages and lymphocyte subgroups in bronchoalveolar lavage fluid *(115,116)*. Repeated exposure to 1128 μg/m^3 for two hours on four days did not change the percentage of neutrophils, total lymphocytes or macrophages in blood and lavage fluid, although small increases in the percentage of killer cells in lavage fluid were observed *(117)*. Repeated exposure for four hours to 3760 μg/m^3 daily for four days *(118)* and for four hours to 3760 μg/m^{3}daily for three days *(119)* was associated with evidence of neutrophilic inflammation. Similar patterns of exposure in healthy volunteers have been associated with increased expression of IL-5, IL-10 and IL-13 in bronchial biopsies, suggesting an upregulation of TH2 cytokines consistent with a pro-allergic effect *(120)*, even when pulmonary function changes are not observed. These authors also observed an increase in expression of ICAM-1, which may indicate a mechanism by which nitrogen dioxide exposure could be associated with increased respiratory infections.

- Exposure to nitrogen dioxide at levels of 3600 μg/m^3 in healthy subjects produced changes in bronchoalveolar lavage fluid consistent with oxidative stress (low levels of uric acid and ascorbate), with evidence of a relatively short-lived (< 24-hour) protective response in the form of increased glutathione levels *(121)*. The initial loss of antioxidants in bronchoalveolar lavage fluid may be attenuated with repeated exposures *(118)*.
- Repeated exposures above 1880 μg/m^3 for two hours per day over three days may be associated with increased susceptibility to infection with influenza virus *(122)*. A three-hour exposure to 1128 μg/m^3 may be sufficient to inhibit the alveolar macrophage response to the influenza virus *(123)*.

Results from controlled exposure to nitrogen dioxide in those with pre-existing lung disease can be summarized as follows.

- People with asthma exposed to 560 μg/m^3 for up to 2.5 hours may experience relatively minor changes in pulmonary function *(124–126)* but this is by no means consistent across studies. Studies with much higher exposures have failed to show any effect *(127)* and some studies showing small effects at lower exposures have been difficult to reproduce *(128)*. Similar inconsistencies have been observed when people with COPD have been studied.
- Two meta-analyses of the association of nitrogen dioxide exposure with bronchial reactivity have been conducted. The first, including studies up to the early 1990s, showed that there was a statistically significant increase in airway hyperresponsiveness to a range of constrictor stimuli following nitrogen dioxide exposure (> 200 μg/m^3 in asthmatics and > 1900 μg/m^3 in healthy controls) *(129)*. A more recent systematic review considered peer-reviewed and non-peer-reviewed original research published up to 2009 and included 41 exposure scenarios from 28 studies *(130)*. Provoking agents included methacholine, histamine, carbachol, cold air and allergens. Nitrogen dioxide exposure was considered in categories of 188–375 μg/m^3, 376–563 μg/m^3, 564–751 μg/m^3, 752–939 μg/m^3, 940–1127 μg/m^3 and 1128–1316 μg/m^3. Overall exposure was associated with increases in airway reactivity and in stratified analyses, associations of bronchial reactivity with exposure were seen within each of the two lowest exposure categories. There was no clear dose–response relationship between the categories. The authors felt the lack of a dose–response effect suggested that nitrogen dioxide did not cause these effects, and that the effect size was too small to be of clinical significance. The lack of a clear dose–response effect is difficult to explain and would argue against a causal relationship. However, for some of the analyses conducted the results are remarkably consistent across studies (I^2 = 0% for the fraction of asthmatics with greater airway hyperresponsiveness following nitrogen dioxide exposure in the lowest and second lowest exposure categories). The small significant increase in airway reactivity associated with low-level exposure could, if borne by a large

proportion of the population, be associated with population-level health effects.

- Included in the meta-analysis by Goodman et al. *(130)* are studies suggesting that exposure to nitrogen dioxide may reduce the threshold of responsiveness to inhaled allergen in those who are sensitized. There was no evidence that the effect of nitrogen dioxide on these specific airway challenges was any different from its effect on response to nonspecific agents. One of the earliest studies to look at this showed that asthmatics sensitized to house dust mites, exposed for 60 minutes to 752 μg/m^3 nitrogen dioxide, had significantly larger falls in FEV_1 in response to house dust mite challenge compared to exposure to air *(131)*. A similar effect was observed in pollen-sensitized asthmatics exposed for 30 minutes to 490 μg/m^3 nitrogen dioxide and then exposed to pollen. After exposure, the falls in peak flow were larger (6.6% difference) and more asthmatics experienced a late asthmatic response, although this latter difference was non-significant *(132)*. Repeated daily exposures of 500 μg/m^3 for 30 minutes for 4 days increased the early- and late-phase falls in FEV_1 following low-dose allergen exposure *(133)*. Simultaneous exposure to nitrogen dioxide (752 μg/m^3) and sulfur dioxide for 6 hours has also been demonstrated to increase response to allergen *(134,135)* . Repeated 30-minute exposures to 500 μg/m^3 nitrogen dioxide are associated with a more pronounced eosinophilic response to allergen challenge, as demonstrated by elevated levels of eosinophilic cationic protein in bronchial washings *(136)* and in sputum and blood *(137)*.
- Exposure to 1880 μg/m^3 nitrogen dioxide for three hours followed by analysis of bronchial lavage fluid has shown that markers of airway inflammation were altered (decreased 6-keto-prostaglandin, increased thromboxane B2 and prostaglandin D2) in those with mild asthma. This was not seen in healthy volunteers, and not seen after exposure to filtered air *(138)*.

Another approach is to directly examine health effects following exposure to cooking with gas. In a chamber study, nine adults and eleven children with asthma were exposed to nitrogen dioxide alone and then nitrogen dioxide with combustion products from a gas heater for a one-hour period *(139)*. Symptoms, lung function and airway reactivity were monitored. Small, clinically non-significant increases in airway reactivity were seen on exposure to 1128 μg/m^3, but this was not seen when exposure occurred with combustion products. The authors concluded these exposures were not associated with clinically relevant health effects.

Overall, these controlled human clinical studies, many of which were conducted more than 20 years ago, have examined the health effects of acute and often very high levels of exposure to nitrogen dioxide rather than the chronic, low-dose exposures experienced by most human populations. Notwithstanding

this, however, they suggest that those who are sensitized or who have asthma may be at particular risk of health effects from exposure to nitrogen dioxide at levels that may be experienced for short periods when individuals are near an unvented combustion appliance.

Epidemiological studies

Identification of studies

Epidemiological studies on health effects of indoor nitrogen dioxide exposure were identified from several electronic searches and by hand searching references in former reviews by WHO *(15)* and EPA *(107)*. Electronic searches were made in PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/), in the ISI Web of Science (http://apps.isiknowledge.com/) and in the LUDOK literature database on air pollution and health effects (http://www.ispm-unibasel.ch/ludok/welcome.html) in January 2009.

We intended to identify all studies with original data on health effects with indoor nitrogen dioxide measurements, and the main descriptors used were "air pollution, indoor", "nitrogen oxides", and "morbidity" or "mortality". We excluded studies that referred to solid fuel use, as this source is often also associated with high levels of particulate matter. We also excluded studies with purely descriptive results or in which no attempt had been made to adjust for potential confounders. In December 2009, a similar search strategy was adopted in order to identify reports published during the period of the review.

We found 72 studies with indoor measurements and evaluation of health effects up to January 2009. Three of these were related to the same study, and here we used the newer results or the publication with the analysis of the most complete sample.

An update of the search found two more publications up to December 2009. Among the remaining 71 studies, we focused on 35 studies on respiratory symptoms and disease, because this outcome was most often significantly related to nitrogen dioxide exposure and permitted the evaluation of concentrations for setting guidelines. Of these 35 studies, 20 were in children, 5 in adults and 10 in asthmatics (children and adults).

In addition, studies that examined the health effects of indoor gas appliances were identified through hand searches of earlier reviews of the topic, citations within the papers identified on health effects of nitrogen dioxide, and papers known to the expert group. We also searched for epidemiological studies on health effects of indoor gas combustion without measurements with the terms "air pollution, indoor", "gas" with "cooking" or "heating", and "respiratory tract diseases" or "lung function".

As there has been some concern that susceptibility may vary with age, the epidemiological studies are presented in two sections – studies in children and studies in adults.

Epidemiological studies in children

Estimates of health effects from studies in which direct measurements of indoor nitrogen dioxide have been made are included in Table 5.2 (see page 280).

Health effects in infants: studies measuring indoor nitrogen dioxide. There have been concerns that infants may be at particular risk of symptoms with high indoor nitrogen dioxide levels because of their high minute volume in relation to body size and because they are likely to spend a large proportion of their time indoors.

However, an early longitudinal study of over 1000 infants up to the age of 18 months living in non-smoking homes showed that the incidence of respiratory illness was not associated with two-week average bedroom nitrogen dioxide levels (22% of nitrogen dioxide levels measured were > 37.6 μg/m^3) *(140)*.

A large cross-sectional study of infants aged 3–12 months taking part in a birth cohort study showed no association of two-week average bedroom nitrogen dioxide (median 12.7 μg/m^3) with respiratory symptoms, including cough, breathlessness and wheezing. Of the 20 infant symptoms examined, only diarrhoea was associated with indoor nitrogen dioxide levels (adjusted odds per doubling of 1.38; 95% CI 1.11–1.70) *(141)*.

More recently, a nested case control study of infants taking part in a birth cohort study was conducted in Oslo, where gas appliances are not used indoors for heating or cooking and levels of indoor nitrogen dioxide are low *(142)*. No association of bronchial obstruction (wheezing, chest recession, rhonchi during auscultation of the chest, forced expiration or rapid breathing, with at least one other episode of "obstructive airways disease") in the first two years of life at living room levels of nitrogen dioxide (arithmetic mean 14.7 μg/m^3; range 2–43 μg/m^3) was seen in 153 matched pairs of cases and controls. However, data from a birth cohort study in Sweden (where, again, indoor gas appliances are rare), using a similar nested case control design, suggested an association of recurrent wheezing up to the age of two years with mean four-week living room nitrogen dioxide *(143)*. There was an increased risk (OR 1.48; 95% CI 0.91–2.42) of wheeze comparing the highest quartile (> 15.6 μg/m^3) to the lowest quartile (< 8.4 μg/m^3), with little evidence of an association below 15.6 μg/m^3. However, the reported associations are below conventional levels of statistical significance. Another study in Scandinavia, but this time based in Copenhagen, showed no association of bedroom nitrogen dioxide levels (mean level 8.6 μg/m^3; 5th centile 3.3 μg/m^3; 95th centile 17.0 μg/m^3, based on up to three ten-week periods of monitoring) with symptoms of wheeze in almost 400 infants born to asthmatic mothers in the first 18 months of life *(144)*.

Populations of infants with higher exposure to indoor nitrogen dioxide were examined in a three-centre birth cohort study. Two-week average (median and 75th centile) living room nitrogen dioxide in each of the three centres (Ashford,

Kent, United Kingdom 10.7 and 16.5 μg/m^3; Barcelona, Spain 86.2 and 112.0 μg/m^3; Menorca, Spain 22.2 and 39.9 μg/m^3) was not associated with wheeze, cough, chestiness or doctor-diagnosed respiratory illness in the first year of life *(145)*. Researchers in the Menorca centre went on to examine associations of neurocognitive status in four-year-old children with level of exposure to nitrogen dioxide as measured at three months *(146)*. A negative association of poor cognition with nitrogen dioxide was observed (a decrease of 0.27 points on a standardized McCarthy Scale measure of cognition per 1.88 μg/m^3). Further, children with increased exposure were at a higher risk of having symptoms of inattention (6% increased risk per 1.88 μg/m^3 increase in nitrogen dioxide). This was particularly seen in children with the GSTP1–Val 105 allele, a genetic polymorphism that may lead to reduced antioxidant defences within the developing brain. In this study, over 70% of children lived in homes with a gas cooker, and almost a quarter had gas fires. The authors stated that confounding by other pollutants such as particulates could not be ruled out, particularly as many of the homes were using bottled gas. Unfortunately, the other centres taking part in the study do not have the necessary outcome information to try to replicate this observation.

Two publications based on a longitudinal study of infants in Connecticut examined lung health and its association with indoor gas appliances and indoor nitrogen dioxide levels *(40,147)*. Participants were selected if, at birth, their mother reported she had another child under the age of 11 years who had asthma. In the 850 infants included in the first report, living in a home with a gas stove was associated with an increased risk of persistent cough (OR 1.52; 95% CI 1.06–2.18) after adjustment for maternal education and a range of household factors including allergen levels, mould and mildew, and smoking in the home. These children had asthmatic siblings and might be considered to be a genetically susceptible group, but the associations were only seen in children whose mother did not have asthma. Forty-five per cent of the infants were living in homes with a two-week average living room nitrogen dioxide level greater than 18.8 μg/m^3, and an association of nitrogen dioxide level with persistent cough was also reported (1.21; 95% CI 1.05–1.40 per 18.8-μg/m^3 increase). In the second report, mothers of about 750 newborn infants recorded each day their infants' respiratory symptoms during the first year of life. Two-week mean living area nitrogen dioxide was measured concurrently with nitrous acid (interquartile range 9.6–32.7 μg/m^3 for nitrogen dioxide, 1.1–4.2 ppb for nitrous acid). In single-pollutant models, a dose-dependent association of the number of days with wheeze, cough and shortness of breath was observed in these infants. Observed associations were most marked for shortness of breath. The adjusted rate ratio for shortness of breath in those with nitrogen dioxide levels > 32.7 μg/m^3 compared to those with levels below 9.6 μg/m^3 was 2.38 (95% CI 1.31–4.38) after adjustment for nitrous acid level. No independent association of symptoms with nitrous acid was seen.

Health effects in children: studies measuring indoor nitrogen dioxide. One of the earliest studies to measure indoor nitrogen dioxide was conducted in the United Kingdom *(148)*. Children living in homes that cooked with gas had more ($P > 0.06$) respiratory illness (positive response to any of cough, wheeze, colds that went to the chest, or asthma or bronchitis in the previous 12 months). In the children who lived in gas-cooking homes, the prevalence of respiratory illness increased with increasing bedroom nitrogen dioxide level: 44%, 59% and 71%, respectively in those exposed to 0–37.6 μg/m^3 , 37.6–75.2 μg/m^3 and 75.2 μg/m^3 ($P < 0.05$). No association of $FEV_{0.75}$, peak flow or mean mid-expiratory flow rate with indoor level of nitrogen dioxide was observed.

Cross-sectional studies were conducted in the Netherlands, where there was concern over the combustion products produced by gas water heaters or geysers. In a study of over 1000 children, no association was observed between respiratory symptoms and lung function measurements (FEV_1, FVC, PEFR, MMEF) and household weekly average nitrogen dioxide level (mean levels 23.6 μg/m^3 for homes without geysers, 40.3 μg/m^3 for homes with vented geysers and 71.7 μg/m^3 for homes with unvented geysers) *(149,150)*.This supported earlier work in the Netherlands showing no association of indoor nitrogen dioxide level with respiratory symptoms *(151)*.

Garrett et al. *(152)* studied children living in Victoria, Australia over a one-year period. Indoor nitrogen dioxide was measured on five occasions in three locations in the home and the frequency recorded of eight respiratory symptoms during the year of observation. Respiratory symptoms were associated with the presence of a gas stove but not with any of the other sources of indoor nitrogen dioxide (gas heaters or smoking in the home). Respiratory symptoms, but not peak flow variability, were more frequent in children with higher bedroom levels of nitrogen dioxide but not kitchen or lounge levels (adjusted odds for any of eight possible respiratory symptoms with bedroom average level > 20 μg/m^3 = 3.62 (95% CI 1.08–12.08) compared to < 10 μg/m^3). The association of respiratory symptoms with a gas stove persisted even after adjustment for bedroom nitrogen dioxide, raising the possibility that the association with gas appliances was not explained by exposure to this pollutant. Interestingly, both the presence of a gas stove and bedroom nitrogen dioxide level were non-significantly more strongly associated with respiratory symptoms in atopic children than in non-atopic children.

In some parts of the world, children's exposure to gas combustion products may be determined or at least strongly influenced by their exposure to gas heaters at school. This has been investigated in Australia. School levels of nitrogen dioxide were monitored during the winter, as were the personal levels of nitrogen dioxide in children who lived in homes with gas sources *(27)*. The winter average six-hourly mean nitrogen dioxide levels in classrooms with an unflued gas heating source ranged from 33.8 to 248 μg/m^3 compared to 13.2–43.2 μg/m^3

in rooms without a gas heater. Several symptoms were investigated (hoarseness, cough with phlegm, dry cough, sneeze, stopped up nose, runny nose, wheeze, sore throat, colds and school absence) but only the mean symptom rate for the latter three showed consistent and significant associations with exposure to > 150.4 μg/m^3 compared to 37.6 μg/m^3. There was some evidence of a dose–response relationship.

One of the most comprehensive assessments was conducted as part of the Six City study. The association of respiratory symptoms with indoor nitrogen dioxide level was examined in more than 1500 children *(153)*, who were followed up for one year. About half of the children lived in homes with a major source (gas stove or kerosene heater). Household annual average levels were determined based on summer and winter measurements made in three household locations, and were 16.1 μg/m^3 for homes without a source and 44.2 μg/m^3 for homes with a source. At the end of follow-up, the annual cumulative incidence of any lower respiratory symptom (shortness of breath, chronic wheeze, chronic cough, chronic phlegm or bronchitis) was higher in those children living in homes with a source (29.0% vs 22.8%) and was higher with increasing annual average indoor nitrogen dioxide (1.40; 95% CI 1.14–1.72 per 28-μg/m^3 increase). Household particulate matter ($PM_{2.5}$) was also measured in this study and included as a covariate in the final analysis. The observed association of incidence of symptoms with both the presence of a gas stove and with increasing indoor nitrogen dioxide level persisted after adjustment for the indoor particle level. In this study, no consistent association of lung function with source or measured nitrogen dioxide was observed. Further analyses were conducted later using regression calibration to include information from children who were not directly measured for nitrogen dioxide but who did have information on surrogate factors such as the presence of a gas appliance *(154)*. Although the authors argued that the estimate, now based on more than 2800 children, was 34% more precise, the effect estimate was little different to earlier analyses (risk of lower respiratory illness over one year, OR 1.5; 95% CI 1.2–1.8 per 28 μg/m^3 increase).

A detailed longitudinal study of the health effects of indoor and outdoor nitrogen dioxide was conducted in schoolchildren in Japan, a country in which the use of gas for cooking is almost universal and where some homes use unvented gas appliances for heating *(10)*. Indoor measurements of nitrogen dioxide were made in summer and winter (mean of the two measurements in homes with vented and unvented appliances were 34.5 and 60.9 μg/m^3, respectively) and outdoor nitrogen dioxide measurements were made at a sampling station based at the child's school (three-year average in each of the six areas involved ranged from 13.2 to 58.3 μg/m^3). There was no association of respiratory symptoms with exposure to gas heaters. At baseline in girls (but not boys), significant associations of indoor nitrogen dioxide with wheeze (OR 1.90; 95% CI 1.30–2.83 per 18.8 μg/m^3), asthma (OR 1.63; 95% CI 1.06–2.54 per 18.8 μg/m^3) and a history of

bronchitis (OR 1.42; 95% CI 1.06–1.90 per 18.8 μg/m^3) were observed even after adjustment for outdoor levels. However, over a three-year period there was no evidence that indoor nitrogen dioxide was associated with incidence of disease, although associations were seen with outdoor nitrogen dioxide level.

Health effects in children: studies measuring personal nitrogen dioxide. Some studies have measured personal nitrogen dioxide rather than indoor levels. The extent with which personal nitrogen dioxide reflects exposure to indoor, compared to outdoor, nitrogen dioxide will vary depending on the time-activity patterns of the child and the frequency and duration of use of indoor sources.

Personal exposure to nitrogen dioxide was measured in children in Hong Kong SAR *(155)*, where indoor sources are common. No association of exposure with symptoms was observed. However, personal exposure was strongly influenced by outdoor levels, with significant differences in personal exposure seen in children who wore samplers during a week of high ambient nitrogen dioxide (40.2 μg/m^3) and those who wore them during a week with lower levels (33.4 μg/m^3).

Personal nitrogen dioxide exposure was measured in 3–4-year-old children in Quebec City, Canada during the winter months and a dose-dependent association of exposure with asthma was reported. Only 6 of the 140 children lived in a home with a gas stove (mean personal exposure with gas stove 32.4 μg/m^3; without gas stove 17.3 μg/m^3). The adjusted OR for case status with the highest level of exposure appears unrealistically high, with very wide confidence levels (24-hour mean of 28.2 μg/m^3 compared to "a zero level"). The unmatched analysis OR was 19.9 (95% CI 4.75 –83.03) while the matched analysis OR was 10.55 (95% CI 3.48 –31.89) *(156)*; this was probably related to the small numbers of children in the risk group.

Personal nitrogen dioxide samplers were worn by Australian primary school children living in Canberra, a low pollution area *(157)*. They were worn from the end of the school day till the following morning, and if the child was taught in a classroom with a gas heater, classroom levels were also measured. Average total personal exposure was low (19.0 μg/m^3) and was not associated with changes in lung function, except for a slightly more pronounced response to a cold air challenge (as measured by change in FEV_1/FVC). There was some evidence that this association was more apparent in children who were *not* mite-sensitized.

One-week average personal exposure was measured in 163 preschool children in Finland *(158)* who attended one of eight day care centres. A small proportion (9.2%) lived in homes with gas appliances (study median 21.1 μg/m^3). However, there was an increased risk of reported cough during the same week as measurement (≤ 16.2 μg/m^3 reference group; 16.2–27.2 μg/m^3, RR 1.23, 95% CI 0.89–1.70; and ≥ 27.2 μg/m^3, RR 1.52, 95% CI 1.00–2.31), particularly in the winter. No clear association with peak expiratory measurements in a subsample

of children (n = 53) was seen. Data from the same study were re-analysed using several methods of defining nitrogen dioxide exposure *(159)*. Overall, statistically significant associations of cough were seen only with personal exposure and in winter, although the direction of association with levels of nitrogen dioxide measured inside the day care centre, outside the day care centre and at a local fixed site was consistent with this observation.

Health effects in children with asthma: studies measuring indoor or personal nitrogen dioxide. Several studies have examined nitrogen dioxide exposure in relation to symptoms of asthma in those with established disease. All have observed increases in some symptoms, but some of the observed associations have not been consistent across the whole population under study.

In Adelaide, Australia, 125 asthmatics wore lapel nitrogen dioxide monitors each day for six weeks while they were at home and kept a symptom diary *(160)*. Time-averaged level of personal exposure to nitrogen dioxide in the home was strongly related to the presence of gas appliances, particularly those in homes with unflued heating appliances (mean average exposure 125 $\mu g/m^3$; interquartile range 50.7–310 $\mu g/m^3$) compared to those in homes using all electric appliances (22.6 $\mu g/m^3$; interquartile range 20.7–28.2 $\mu g/m^3$). In participants under the age of 14 years, there was an association of personal exposure level with symptoms of chest tightness (OR 1.29; 95% CI 1.16–1.43 per standard deviation increase in nitrogen dioxide, which in this study was 48.3 $\mu g/m^3$), breathlessness (OR 1.13; 95% CI 1.0–1.28 with a one-day lag) and asthma attacks. In adults, only one isolated association of one of the seven symptoms investigated was associated with nitrogen dioxide, and this was seen only after accounting for a one-day lag.

Personal exposure to nitrogen dioxide was measured in 45 asthmatic children over a 10-day period by Delfino et al. *(161)* in Seattle. The children, aged 9–18 years, were also subject to daily measurements of airway inflammation (exhaled nitric oxide) with a personal active sampling device. Increases in fractional exhaled nitric oxide (FENO) were seen with $PM_{2.5}$, elemental carbon and nitrogen dioxide (for each 32-$\mu g/m^3$ increase in nitrogen dioxide, an increase of 1.6 ppb FENO (95% CI 0.4–2.8)). Positive associations were seen only in those who were taking anti-inflammatory medication, which may reflect the severity of the underlying disease. In this population, there was a wide range of personal exposure (5.1–198.7 $\mu g/m^3$). Daily lung function measurements were also made *(162)*. Personal nitrogen dioxide was associated with decrements in lung function, the change in FEV_1 as a percentage of predicted FEV_1 being 2.45 (95% CI 3.57 –1.33) per 32-$\mu g/m^3$ increase in nitrogen dioxide. Lung function associations were more clearly seen in those children who did not use a bronchodilator. These associations were robust to adjustment for personal $PM_{2.5}$ exposure, but the authors in their discussion suggest that the association with nitrogen dioxide may be due to confounding by another toxic pollutants from traffic.

A larger study conducted in eight inner-city areas in the United States (Bronx, NY; East Harlem, NY; St Louis, MO; Washington, DC; Baltimore, MD; Chicago, IL; Cleveland, OH; and Detroit, MI) recruited children attending accident and emergency departments for the treatment of asthma, measured indoor nitrogen dioxide in the children's bedrooms (median 56.0 μg/m^3; range 0.9–902.4 μg/m^3) and gathered health information at baseline and three, six and nine months later *(23)*. Three respiratory outcomes were considered: (*a*) more than four days in the last fortnight with symptoms; (*b*) unscheduled visits to health care providers; and (*c*) peak flow less than 80% of predicted. Associations of these outcomes with nitrogen dioxide were modified by atopic status and by season. Nitrogen dioxide levels in the highest quartile (cut-off not given) were associated with more than four days with symptoms compared to those exposed to lower levels, but this was only in children who had *negative* skin tests. No association was seen in those who were skin-test-positive to at least one of 16 common indoor and outdoor aero-allergens. The overall difference in indoor nitrogen dioxide level in warm and cold months was relatively small (6.8 μg/m^3) but low peak flow was associated with nitrogen dioxide only in the colder months. The authors postulate that this may reflect increased susceptibility to infections during the colder months. However, as children spend more time indoors when it is cold, the association may have arisen because of the closer correlation of indoor measurements with personal measurements in the winter period.

A total of 150 inner-city children with asthma, predominantly African Americans, were studied over a six-month period in Baltimore, United States *(26)*. Although at baseline the average indoor nitrogen dioxide level was similar in the homes of asthmatic children and a control group of non-asthmatic children *(163)*, there was evidence that indoor nitrogen dioxide was associated with symptoms in the asthmatic children. Assessment of bedroom indoor nitrogen dioxide and indoor $PM_{2.5}$ was made on three occasions (overall mean of average seven-day indoor nitrogen dioxide 56.4 μg/m^3) and caregivers were asked to report symptoms that had occurred in the previous fortnight. There was a significantly increased risk of reporting symptoms with increasing nitrogen dioxide levels (e.g. adjusted incident rate ratio for speech-limiting wheeze 1.17 (95% CI 1.08–1.27) per 37.6-μg/m^3 increase in nitrogen dioxide) and these associations were present even after adjustment for indoor particulates. No association was observed for other outcomes such as medication use or use of health services. About two thirds of the children were atopic as assessed by skin tests, but in general the presence of atopy did not modify the associations observed. However, nocturnal symptoms were more strongly related to nitrogen dioxide levels in atopic children (incidence rate ratio 1.13 per 37.6 μg/m^3 increase in nitrogen dioxide) compared to non-atopic children (incidence rate ratio 1.03 per 37.6 μg/m^3 increase in nitrogen dioxide). About 83% of these homes had gas stoves for cooking and 12% reported they used their stove for heating the home.

The association of symptoms in children with asthma with the use of gas appliances and indoor nitrogen dioxide level may be different in different housing conditions. In Connecticut and south-west Massachusetts in the United States, the reporting of wheeze and chest tightness in the month prior to indoor nitrogen dioxide sampling (mean 10-day average living room nitrogen dioxide 16.2 $\mu g/m^3$ in homes without a source and 48.7 $\mu g/m^3$ in homes with a source) in children with asthma was significantly associated with the presence of a gas stove and with increases in nitrogen dioxide levels as measured in the main living area. However, this association was only seen when analyses were limited to children living in homes that were in "multi-family" housing and were not seen in single-family housing *(164)*. Among these children in multi-family homes, exposure to gas stoves increased the likelihood of wheeze (OR 2.27; 95% CI 1.15–4.47), shortness of breath (OR 2.33; 95% CI 1.12–5.06) and chest tightness (OR 4.34; 95% CI 1.76–10.69) and each 37.6-$\mu g/m^3$ increase in nitrogen dioxide increased both likelihood of any wheeze (OR 1.52; 95% CI 1.04– 2.21) or chest tightness (OR 1.61; 95% CI 1.04– 2.49), and days of wheeze (RR 1.33; 95% CI 1.05–1.68) or chest tightness (RR 1.51; 95% CI 1.18–1.91). These multi-family homes were smaller, the implication being that main living room levels of nitrogen dioxide may better reflect the child's bedroom level. Multi-family homes had higher levels of nitrogen dioxide (45% recording two-week averages of > 37.6 $\mu g/m^3$ compared to only 9.3% in the single-family homes). Children included in this study were the siblings of the infants recruited into the study reported by Belanger et al. *(147)* and Van Strien et al. *(40)* and described earlier in this chapter.

One possible mechanism to explain the association of indoor nitrogen with asthma may be an increased susceptibility to severe or prolonged infection. In England, 112 children with asthma were followed up for almost a year, during which period they kept an asthma diary and measured their personal exposure over each seven-day period using Palmes tubes *(165,166)*. When asthma exacerbations occurred, nasal aspirates were taken to confirm the presence of a viral infection.

The geometric mean exposure to nitrogen dioxide at the time of infection was 10.6 $\mu g/m^3$. Compared with exposures of < 8 $\mu g/m^3$, exposures of > 28 $\mu g/m^3$ were associated with an increased risk of asthma following infection (RR 1.9; 95% CI 1.1–3.4). The risk of experiencing an episode of lowered peak expiratory flow after having experienced symptoms highly suggestive of infection increased in a dose-dependent fashion with increasing nitrogen dioxide levels at the time of the infection. The increase in symptom score and the decrements in peak flow experienced during the laboratory-confirmed viral infection were larger in children who had higher exposures measured in the week prior to the start of the exacerbation. Although the average personal nitrogen dioxide was lower than in some studies, it was strongly related to the presence of gas appliances in the home and 23 of the children had at least one measurement in

excess of 100 μg/m^3 (32 of the measurements of the seven-day average personal exposure were > 100 μg/m^3).

These observations that children with asthma have worse symptoms if exposed to higher levels of indoor nitrogen dioxide suggest that their removal from exposure should lead to amelioration of their symptoms. However, few interventional studies have been reported. In recognition that classroom levels of nitrogen dioxide (largely determined by the use of unflued gas heaters) are an important source of exposure, an intervention study was conducted in Australia. Researchers assessed the effect of changing from unflued gas heaters in school classrooms to flued gas heaters or electric heaters *(167)*. Almost 200 asthmatic children in 10 control schools, 4 schools that had changed to flued gas heaters and 4 schools that had changed to electric heaters were followed for a period of 12 weeks. Following the intervention, the mean rate of symptoms of difficulty breathing during the day and at night, chest tightness and asthma attacks during the day was lower in children attending intervention schools. No change in lung function parameters was observed. Six-hourly average classroom levels of nitrogen dioxide ranged from 13.2–71.4 μg/m^3 (intervention) to 22.5–218.1 μg/m^3 (control) during the period of follow-up.

In further studies, 174 of these children with asthma kept a symptom diary over a 12-week period *(168)*. Home (kitchen) and classroom nitrogen dioxide levels were measured (indoor daily range: classroom 16.9–577.2 μg/m^3; kitchens 5.6–795.4 μg/m^3) and the association of several symptoms with the maximum of three daily time-averaged kitchen and classroom levels was assessed. Difficulty in breathing at night was associated with school (adjusted relative rate 1.11 (95% CI 1.05–1.18) per 18.8- μg/m^3 increase in nitrogen dioxide) and home levels (adjusted relative rate 1.03 (95% CI 1.01–1.05) per 18.8 μg/m^3 increase), while associations with nocturnal chest tightness and nocturnal asthma were seen only for school (adjusted relative rate 1.12 (95% CI 1.07–1.17) per 18.8-μg/m^3 increase in nitrogen dioxide) and home level (adjusted relative rate 1.04 (95% CI 1.00–1.07) per 18.8-μg/m^3 increase), respectively. Decrements in lung function (mean FEV_1 % predicted) were observed (–0.39% per 18.8 μg/m^3 increase in nitrogen dioxide level in the kitchen). At the time of the study, mattress house dust mite levels were assessed; there was no evidence that the association of nitrogen dioxide with symptoms was modified by mattress allergen levels.

Another intervention study was conducted in New Zealand *(169)*. Parents of children with asthma, living in homes heated by an unflued gas heater or a plug-in electrical heater, were invited to alter their current heating system to either a heat pump, a wood pellet burner or a flued gas heater. All eventually received their heater of choice, but they were randomized to receive them immediately (treatment group) or after one year (control group).

Improvements in subjective markers of health as reported by parents (sleep disturbed by wheeze, dry cough at night, overall health) symptoms reporting

in diaries (cough at night, wheeze at night) and health service utilization (visits to the doctor, visits to the pharmacist) were seen in the treatment group but no change in objective markers such as peak flow variability or lung function tests were seen. During the period of the study, the levels of nitrogen dioxide in the bedrooms and living rooms of the intervention group were 8.5 and 7.3 μg/m^3, respectively, compared with the levels in the control group of 15.7 and 10.9 μg/m^3, respectively (both $P > 0.001$). However, the intervention houses were also warmer (0.57 °C and 1.1 °C for the bedroom and living room, respectively) and therefore health status may have been higher owing to increased warmth rather than decreased nitrogen dioxide levels.

The Hasselblad meta-analysis. In the early 1990s, Hasselblad et al. published a meta-analysis of the association of indoor nitrogen dioxide levels with respiratory illness in children *(170)*. This report was one of the earliest examples of the use of meta-analysis for synthesizing evidence from studies of environmental hazards. It included published studies that had measured either indoor nitrogen dioxide or the use of a gas appliance as the exposure metric and combined the results from 11 studies, presented in 15 different publications from the Netherlands *(150,171)*, the United Kingdom *(148,172–178)* and the United States *(153,179–182)*.

In studies in which gas stoves rather than measured nitrogen dioxide represented the exposure, it was assumed that the average nitrogen dioxide exposure was about 30 μg/m^3 higher in homes with a gas stove than in those without one. Respiratory symptoms were any respiratory symptom, with some variation between studies but including wheeze, cough, coughs going to the chest, shortness of breath and bronchitis. In children under the age of 12 years, a 30-μg/m^3 increase was equivalent to a 20% increased risk of symptoms. Exclusion of studies in which gas stoves were the proxy markers for exposure led to an increase in effect size (OR 1.27 per 30-μg/m^3 increase). This analysis is of considerable importance, as it provided the basis for outdoor air quality guideline setting by WHO in 1997 *(183)* and its conclusions have, to date, not been seriously challenged by any new evidence. Extrapolating directly from the Hasselblad meta-analysis, WHO in 1997 reported that "On the basis of a background level of 15 μg/m^3 (0.008 ppm) and the fact that significant adverse health effects occur with an additional level of 28.2 μg/m^3 (0.015 ppm) or more, an annual guideline value [for outdoor nitrogen dioxide] of 40 μg/m^3 (0.023 ppm) is proposed. This value will avoid the most severe exposures."

Epidemiological studies in adults

In comparison to the number of studies in children, there are relatively few studies that have reported associations of adult respiratory health with indoor nitrogen dioxide levels.

Health effects in adults: studies measuring indoor nitrogen dioxide. Indoor nitrogen dioxide measurements were made in a subsample of households taking part in a longitudinal study in the United States (mean 24-hour average 94.0 μg/m^3 in homes using gas for cooking and 37.6 μg/m^3 in those using electricity). No association of respiratory illness in any member of the household (including adult members) with measured nitrogen dioxide level was observed *(180)*.

A cohort of 152 non-smoking women living in Vlagtwedde and Vlaardingen in the Netherlands was studied in 1982. Time-activity patterns showed that the women spent about 25% of their time in their kitchens, 25% in the lounge and 35% in the bedroom *(184)*. Most (97) of the women had also had their FEV_1 measured and, in general, decrements in FEV_1 were associated with increases in indoor nitrogen dioxide levels, the largest estimates being seen for measurements in the bedroom (mean deficit in FEV_1 2.38 ml per μg/m^3 increase in nitrogen dioxide; $P < 0.01$) and the lounge (mean deficit in FEV_1 3.91 ml per μg/m^3 increase in nitrogen dioxide; $P > 0.05$) rather than the kitchen (mean deficit in FEV1 0.69 ml per μg/m^3 increase in nitrogen dioxide; $P > 0.05$) *(185)*. Although there was some evidence that increasing nitrogen dioxide level was associated with the decline in FEV_1 that had been recorded in these women over the previous 13 years, this association failed to reach conventional levels of significance. Effect modification by atopy or asthma was not considered.

In Hong Kong SAR, mothers of children taking part in a large study of respiratory health wore personal nitrogen dioxide badges for a 24-hour period *(155)*. Personal nitrogen dioxide was higher in women if they cooked more frequently, but only among those who did not ventilate their kitchen by the use of an extractor fan. In users of LPG or kerosene, the mean personal 24-hour average exposure was 37.7 μg/m^3 if the kitchen was ventilated during cooking and 41.7 μg/m^3 if the kitchen was unventilated. There was no consistent association of personal nitrogen dioxide with frequency of cooking or presence of ventilation fans in the children living in these homes, probably reflecting their different time-activity patterns. Personal nitrogen dioxide was higher in women who cooked with LPG compared to those using piped gas.

There was some evidence that personal exposure levels may be associated with chronic cough and allergic rhinitis. The mean personal 24-hour average exposure was 42.3 μg/m^3 in women with cough and 35.9 μg/m^3 in those without ($P = 0.05$), while it was 42.4 μg/m^3 in women with allergic rhinitis and 35.5 μg/m^3 in those without ($P = 0.002$).

Women who had recently given birth were recruited into a study in which health information was collected at baseline and the presence of respiratory symptoms regularly collected every two weeks for a year *(186)*. Indoor nitrogen dioxide measurements were made with passive samplers over a two-week period in the winter and this was repeated depending on whether gas or kerosene appliances were present. Even though this was a large study involving 888

non-smoking women, no association of nitrogen dioxide level with symptoms of wheeze, chest tightness, hoarseness or phlegm was seen when nitrogen dioxide was considered as a continuous variable. When it was dichotomized, however, to compare the top quartile (> 150.4 μg/m^3) with the lower three quartiles, household levels were associated with chest tightness (1.94; 95% CI 0.98–3.85) and with wheeze (4.00; 95% CI 1.45–11.0). An association of symptoms with the use of kerosene heaters was reported and this may have been due to the sulfate emissions from these heaters.

Indoor nitrogen dioxide levels were measured for one week in the homes of 148 people with severe COPD living in north-eastern Scotland *(187)*. Half of the homes had at least one active smoker, and nitrogen dioxide levels were higher in homes with smokers (median 16.2 μg compared to 12.9 μg; $P < 0.02$) and no association of symptoms or specific respiratory quality of life was observed.

Kitchen, living room and bedroom nitrogen dioxide levels were measured for one week in the summer and one week in the winter in urban (Pisa) and rural (Po Delta) areas of Italy *(188)*. Mean kitchen levels of nitrogen dioxide were statistically different in the two regions (54.5 vs 62.0 μg/m^3 ($P < 0.05$) in winter and 41.4 vs 37.6 μg/m^3 ($P < 0.01$) in the summer for Pisa and the Po Delta, respectively). An average personal exposure in adults was generated from time-activity patterns. Exposure above the study median nitrogen dioxide index was associated with an increased risk of acute respiratory symptoms (OR 1.66; 95% CI 1.08–2.57) but no association was seen for bronchitic/asthmatic symptoms.

Those who cook in the home and professional cooks are exposed to high levels of nitrogen dioxide as well as to other cooking-related pollutants. There is no evidence from large-scale epidemiological studies that have measured indoor nitrogen dioxide levels that respiratory health is worse in those who regularly use unvented gas appliances for cooking. In a cross-sectional study of 37 professional cooks (mainly women) working in four large hospital kitchens in Brazil *(189)*, average daily levels of nitrogen dioxide in one kitchen reached almost 188 μg/m^3. The authors presented tabulated coefficients from regression models to suggest total exposure to nitrogen dioxide (the product of years working in that kitchen times the level of nitrogen dioxide in the kitchen) was associated with lower levels of forced expiratory flow ($P < 0.031$), even after adjustment for smoking behaviour and the presence of asthma, but it is difficult to interpret the effect estimates from this. Confounding by other cooking-related pollutants cannot be ruled out.

Presence of gas appliances at home as an indicator of nitrogen dioxide exposure

In setting guidelines for indoor air quality, there is clearly a need for direct measurements of nitrogen dioxide levels, and for these levels to be associated with some health impairment. In the indoor setting, however, where the source of indoor nitrogen dioxide may, in the main, be from indoor gas appliances, the pres-

ence of the appliance itself may act as a proxy marker of exposure. Of particular concern is that the use of some appliances, particularly gas cookers (which are unvented) is associated with short-lived peaks of exposure that are not captured or measured by most of the monitoring techniques used in epidemiological studies. Controlled exposure studies suggest that nitrogen dioxide at levels associated with these peaks may be harmful but studies that use "average nitrogen dioxide" may not be able to detect these health effects. Under these circumstances, association of a health effect with the presence and use of the gas appliance may provide stronger evidence of health effects of indoor nitrogen dioxide than measurements of the gas itself.

However, there are three major pitfalls with this approach. First, a simple exposure metric of "exposed to a gas appliance" does not capture potential variation in the nature or intensity of the exposure, which may vary with frequency of use, intensity of use, use of extractor fans, household ventilation, the proximity to the appliance and the contribution of this source to the individual's total exposure. This may explain the heterogeneity in the results of studies. Second, examination of dose–response effects may be difficult as "frequent use" of a gas cooking appliance also implies frequent exposure to a range of other cooking-related pollutants. Third, and related to the previous point, the group selected for comparison should ideally comprise a group that uses electricity. This may be difficult in countries where gas is used almost universally – for example, until more recently in Hong Kong SAR and Italy. In these circumstances, studies often report comparisons of "frequent users" with "less frequent users".

There are many more studies on the association of health with the presence of gas appliances than with measured nitrogen dioxide and they are of varying quality. While cross-sectional studies are of interest in making a causal inference, greater weight would naturally be placed on those that are longitudinal in design. Further, in older children and adults, objective markers of disease such as lung function may be used and these measurements, in well-designed studies, could be argued to provide better evidence for associations than those that are based on self-reported symptoms. However, respiratory disease may occur in the absence of measurable change in lung function parameters.

Health effects: studies measuring acute health effects of exposure to gas appliances. The acute effects of direct exposure to gas combustion have been studied in people's homes. An early pilot study that used this approach reported change in FVC in asthmatic and non-asthmatic women in whom continuous measurements of nitrogen dioxide were made during cooking at home over a five-day period *(190)*. Spirometric measurements were made before, during and after each cooking period. The highest average nitrogen dioxide level reached was about 1500 $\mu g/m^3$ (0.8 ppm) and the highest five-minute average level was about 1692 $\mu g/m^3$ (0.9 ppm). No formal statistical analyses were presented but in the asth-

matic women, decrements in FVC were seen when cooking with gas on many of the cooking occasions, and when nitrogen dioxide levels reached over 564 μg/m^3 (mean or five-minute average) nearly all asthmatic women showed a drop in FVC. This was not seen in the non-asthmatic women, but it should be noted that the peak nitrogen dioxide levels for the non-asthmatic group were not as high (no reason was given for this). The magnitude of the change in FVC reported in the asthmatic women was substantial, some individuals showing a 10% change in FVC and one individual on one occasion showing a change of 20%.

In another study, 16 adult non-smoking women with asthma had their peak flow measured before and after cooking with gas in their own homes. The fall in peak flow after cooking was related to the level of nitrogen dioxide recorded during cooking (highest peak exposure 500 μg/m^3) and over a two-week period their personal exposure to nitrogen dioxide (range 37.3–135.6 μg/m^3; mean 80.49 μg/m^3) was associated with increased use of salbutamol *(191)*.

Health effects in children: cross-sectional studies looking at exposure to gas appliances. Cross-sectional studies conducted more than 25 years ago suggested that the use of gas cooking was associated with increased hospital admissions for respiratory disease in preschool children in the United States *(179)* and more respiratory symptoms in schoolchildren in England *(174)* and the United States *(192–194)*. Participants in the United Kingdom study were followed for about five years and there was some evidence that the association became less apparent as the children became older *(177)*. Other cross-sectional studies conducted at a similar time did not observe these associations *(180,182,195)* and a longitudinal study in which children were studied for one year to identify episodes of respiratory illness also found no association *(181)*. Many, but not all, of these early studies made attempts to adjust for potential confounding by social class, parental smoking and other household factors, recognizing that the use of gas appliances, in some communities at least, was strongly related to lower socioeconomic status and increased rates of parental smoking *(179)*.

In cross-sectional studies conducted more than 25 years ago, non-significant ($P > 0.05$) decrements in $FEV_{0.75}$ were reported in children living in homes that cooked with gas *(193)*. Hosein et al. *(196)* reported decrements in FEV_1 with the use of a gas stove in 1357 children living in the United States, but this study collected information on eight household factors (pet keeping, hobbies that exposed residents to gases/vapours/dust, cooking fuels, heating system, presence of a fireplace, use of humidifiers or air conditioning, domestic crowding and smokers in the household) and there were significant interactions between some of them, making the overall effect of gas stoves difficult to interpret. Ekwo et al. *(179)* administered isoprenaline to children and examined differences in response in children with different household exposures. Greater bronchodilator responses were observed in children exposed to tobacco smoke than in those who were not

exposed, but no such difference was seen in children exposed to gas cooking appliances, even though an association of symptoms with the use of gas had been observed.

In the past, unvented gas water heaters were relatively common indoor gas appliances in the Netherlands, and researchers have examined their effect on children's health. Lung function was measured by spirometry and a forced oscillation technique in 470 primary school children *(197)*. Respiratory symptoms were non-significantly ($P > 0.05$) more common in children living in homes with unvented gas water heaters. There was no clear, consistent association of spirometric indices or of measurements of impedance with the use of these appliances, although the small observed differences were in the expected direction and were greater for measurements of resistance and impedance in girls.

Large-scale cross-sectional studies have been conducted more recently. In Canadian schoolchildren (n = 10 819), the presence of a gas cooking stove in the home was associated with current asthma (OR 1.95; 95% CI 1.4– 2.68) but not with "wheezing syndrome" after adjustment for a variety of household (e.g. damp, environmental tobacco smoke) and socioeconomic (parental education) confounders *(198)*. A study in eastern Germany conducted in 1992/1993 showed an increased risk of "cough without a cold" (OR 1.63; 95% CI 1.23–2.04) and other cough symptoms in over 2000 children aged 5–14 years living in homes with a gas cooker *(199)*. The lifetime prevalence of other symptoms was not increased. White blood cell counts were increased in children in homes with gas cookers, particularly in those likely to be exposed to high levels of gas-cooking-derived pollutants (those in homes with no extraction fans or smaller homes, and children who spent more time indoors). There was a suggestion that this latter association may be stronger for bottled gas than for the town gas that was in use at the time. In 4–5-year-old Australian children, the use of a natural gas stove was associated with an increased risk of wheeze, asthma and colds *(200)*. In the Third National Health and Nutrition Examination Survey, use of a gas stove for cooking or for heating was associated with an increased risk (OR 1.8; 95% CI 1.02–3.20) of physician-diagnosed asthma in children under the age of six years *(201)*. However, in a large (n ~ 28 700) study of children aged 6–9 years living in Austria and taking part in the International Study of Asthma and Allergies in Childhood (ISAAC, Phase 1), the 12-month period prevalence of wheeze was not associated with gas cooking, although associations with other indoor risk factors such as environmental tobacco smoke, dampness and mould were seen *(202)*.

Effect modification by allergic predisposition, as shown by total IgE levels, on the association of lung function with exposure to gas has been observed in a cross-sectional study of adolescents. Corbo et al. *(203)* studied teenagers in Italy, where the use of gas for cooking is almost universal, and asked them how much time they spent in the kitchen. More girls than boys reported they were "often in the kitchen while their mother cooked" and in girls but not boys those who

reported being "often in the kitchen" had worse lung function as measured by forced expiratory flow rate than those who were in the kitchen only "some of the time". This association was observed mainly in girls with total IgE above 48.6 IU/ml (the median value in girls), suggesting the effect may be greater in girls who are atopic. Effect modification by total IgE level persisted even if children with positive skin tests were excluded. This study suggests a dose-dependent association of exposure to gas cooking with airway function that is modified by both atopy and gender in this age group. It also suggests that proximity to the gas cooker at the time of its use rather than "living in a home with a gas cooker" is the exposure associated with symptoms. However, confounding by exposure to cooking fumes or other pollutants from gas combustion cannot be ruled out.

An analysis of information collected from asthmatic children taking part in the National Health and Nutrition Examination Survey showed that girls who lived in a home with a gas stove (about 45% of the sample) had lower lung function (FEV_1, FEF_{25-75}, FEV_1/FVC) than those who did not *(204)*. However, this association was only seen in girls who did not take asthma medication and was not seen in boys.

The association of respiratory symptoms with gas for cooking may be modified by levels of outdoor nitrogen dioxide. This was examined in a small study in Hong Kong SAR, where cooking with gas (piped town gas and LPG) is almost universal. Children living in two contrasting areas were examined *(205)*. In an area with relatively low background pollution (nitrogen dioxide annual mean 45 $\mu g/m^3$), current doctor-diagnosed "respiratory illness" was more common in children living in homes that cooked most frequently with gas. This dose–response relationship to gas cooking was not observed in a nearby area with higher outdoor background levels of particulate matter and oxides of nitrogen (nitrogen dioxide annual mean 59 $\mu g/m^3$), suggesting that in multicentre studies the association of gas cooking with symptoms may vary with level of ambient pollutants.

Using a case-control design, the association of severe asthma (children whose parents reported that they suffered either 12 or more wheezing attacks in the past 12 months or an attack of wheeze over the same period that limited speech to only one or two words at a time between breaths) with use of gas for cooking was examined *(206)*. Controls were children with no history of asthma or wheezing at any age. There was no evidence that the use of gas for cooking differed between cases and controls (adjusted OR 0.86; 95% CI 0.61–1.23).

Health effects in children: longitudinal studies looking at exposure to gas appliances. A longitudinal study design has been adopted in some studies to examine the health effects of exposure to gas appliances in infancy. Primigravida mothers were interviewed early in pregnancy regarding household characteristics, and the health visitor information on their offspring (n = 1565) was collected at one year of age *(178)*. Although the proportion of children with a respiratory illness

and with an admission to hospital for respiratory illness was higher in homes with gas cooking, the difference was not significant.

The association of exposure to gas appliances in infancy to later respiratory health was examined in Australia, where gas heaters are the main source of indoor combustion products. As part of the Tasmanian Infant Health Survey, the type of heating appliance in use in infancy was recorded and, at the age of seven years, information on respiratory symptoms was collected *(207)*. Only a small proportion of the children lived in homes with a gas heater (most likely to have been fuelled by LPG) but this small group had a substantially increased risk of asthma in later life (1.92; 95% CI 1.33–2.76), even after adjustment for some markers of socioeconomic status (maternal education) and household smoking. In the same publication, the authors presented results from an extended analysis involving more than 6000 children, in which they noted a cross-sectional association of recent wheeze (OR 1.41; 95% CI 1.17–1.71) and asthma (OR 1.33; 95% CI 1.12–1.57) with current use of gas heaters.

Another publication using data from the same children looked at the association of gas use in infancy with lung function *(208)*. Those who had lived in a home with either a gas heater or a gas cooker in infancy were more likely to be sensitized to house dust mites and had a lower FEV_1. In the children included in this analysis, the association of asthma with the use of gas was below conventional levels of significance. However, airway obstruction was more strongly associated with current gas cooking in children sensitized to house dust mites than in those not sensitized.

The long-term health effects of exposure to gas appliances was also examined in a United Kingdom study that measured prevalence of wheeze in teenagers in relation to exposure to gas cookers as a child *(209)*. Almost 2000 children provided information on symptoms at ages 7–8 and 15–17 years and, in addition, at the age of 16–18 years reported their use of gas appliances (for cooking or heating) in their current home and in their home when they were a child. Childhood wheezing was associated with childhood exposure to any gas appliance and with childhood exposure to a gas hob (OR 1.47; 95% CI 1.05–2.04). However, childhood exposure to gas appliances was not associated with wheeze that persisted into the teenage years. Wheeze in adolescence was not associated with current teenage exposure and, surprisingly, persistent wheeze was less frequent in those exposed to gas in the teenage years. The authors argued that this latter observation might be explained by selective avoidance.

A similar age group was studied as part of a longitudinal study in southern California *(210)*. Participants aged 9–16 years were recruited and followed for five years or until graduation. Excluding those with "ever physician-diagnosed asthma" at baseline, the association of indoor factors with doctor-diagnosed asthma was examined in the remaining 3535 children. In this group, at baseline, the use of gas for heating and for cooking was common and more commonly

reported by those who had wheeze (78% of those with wheeze and 73.8% of those without wheeze used gas for heating ($P = 0.004$), while 79.4% of those with wheeze and 77.7% of those without wheeze had a gas stove ($P = 0.27$)). Over the five-year period, there was no evidence that the presence of these appliances was associated with the incidence of physician-diagnosed asthma in children with or without wheeze at baseline.

Longitudinal studies have been used to examine whether exposure to gas appliances has a deleterious effect on lung growth in children. In Arizona, United States, a four-year study was conducted to determine whether living in a home where gas was used for cooking was associated with poor lung growth in children aged eight years at baseline. Despite strong cross-sectional associations of the use of gas for cooking with symptoms of wheeze, cough and sputum production at baseline, there was no evidence that exposed children had lower rates of lung growth than unexposed children *(192)*.

These findings are supported by work conducted as part of the Six Cities Study in the United States. First reports from the study suggested that exposure to gas stoves was associated with reduced lung function in children *(194)*. Later work suggested that a reduction of 0.7% in mean FEV_1 and 0.6% in mean FVC seen in the first examination was not observed after three years of follow-up, where a non-significant reduction of 0.3% in both measurements was seen *(182)*. After further examination, analyses based on 7834 children aged between six and ten years who had between two and five annual measurements of lung function showed no effect of the use of a gas stove on pulmonary function level at the end of the study *(211)*.

As part of the meta-analysis conducted by Hasselblad et al. *(170)* in the early 1980s, the association of childhood respiratory illness with the use of gas for cooking was determined to be 1.15 (95% CI 1.09–1.22).

Health effects in adults: cross-sectional studies looking at exposure to gas appliances. If we hypothesize that the health effects of combustion products such as nitrogen dioxide from unvented gas appliances depend on repeated high exposures, those that actually use the appliances and are therefore exposed to these peaks would be expected to be at greatest risk. In most communities, cooking remains a task largely performed by women and particularly by young and middle-aged women with large families. This being so, we might expect women to be at particular risk. However, one of the first studies examining the association of the use of gas with respiratory health suggested the opposite. In a community-based representative sample of almost 2000 adults in Maryland, United States, men living in homes with a gas cooker had more chronic cough and wheeze with breathlessness than those living in homes with electric cookers. No association was seen in women. The authors hypothesized that women have, over thousands of years, been exposed to pollutants generated by cooking and heating and have

an evolutionary advantage over men in being resistant to the health effects of exposure to fumes from cooking and cooking appliances *(212,213)*.

A small case-control study was conducted shortly afterwards. The type of cooker that was used by 102 non-smokers with FEV_1 in the highest quartile of the distribution was compared with that used by 103 non-smoking women with FEV_1 in the lowest quartile *(214)*. Exposure to gas appliances was non-significantly higher in those with low lung function (30.4% vs 22.3%; OR 1.82; P = 0.076) and cooking with gas for more than 10 years was more common in those with low lung function. Effect modification by atopy or frequency of use was not examined.

Large-scale cross-sectional studies conducted more recently in the United States suggest little association of symptoms with use of gas in either men or women. For example, in the National Health and Nutrition Examination Survey III (NHANES III), the association with gas stove use was examined in 7630 lifelong non-smokers (mean age 42 years) *(215)*. There was no association of current gas stove use with symptoms of phlegm, wheeze or dyspnoea, although an association with chronic cough was seen (OR 1.6; 95% CI 1.1–2.3). In fact, those who had a gas stove appeared to have *better* lung function than those who did not. These analyses were extensively adjusted for other household and sociodemographic factors. Effect modification by gender (and by atopy as measured by skin tests) was tested and was not observed.

Nevertheless, an analysis of data collected as part of the ECRHS multicentre study presented evidence that respiratory symptoms suggestive of asthma, and lung function changes suggestive of airway obstruction, may be associated with the use of gas cooking in some communities *(216,217)*. A strong cross-sectional association of respiratory symptoms with the use of gas for cooking was seen in women, but not men, living in three towns in England. The association was particularly strong in women (P for interaction < 0.05). Women who were sensitized to one of four common aero-allergens were particularly at risk, although formal tests for effect modification by atopy in women were not significant (P for interaction > 0.05). These observations were supported by decrements in FEV_1 and FEV_1/FVC. As part of the ECRHS, the same protocol was followed in other research centres in Europe. However, when the same statistical approach was extended to include these centres, considerable heterogeneity was observed between centres with the strongest effects being seen in the United Kingdom centres. No explanation for this heterogeneity was found but it may have been due to the varying exposure suggested by reporting that a participant "mainly uses gas for cooking". In this early study no information on frequency of use, use of natural ventilation, type of gas used and maintenance of appliances was collected.

Researchers in the Netherlands *(218)* looked for effect modification by atopy on the association of gas cooking with bronchial reactivity. The protocol adopted for the study was that of the ECRHS but the age range studied was larger (20–70

years). Atopy was defined by the presence of specific IgE to common aero-allergens and measured bronchial reactivity to methacholine. There was no evidence that atopics had greater bronchial reactivity if they used gas for cooking, but the associations were much stronger in both men and women who had high total IgE compared to those with low total IgE. The authors argued that total IgE was a superior way of identifying the susceptible "atopic" subgroups but to date their findings have been supported only by the study of adolescents in Italy *(203)*. Total IgE is higher in smokers *(219)* and in those exposed to "gas, dust, fumes or mists" in the workplace *(220)*. None of these authors considered whether total IgE was higher in those who cooked with gas and was a surrogate marker for greater exposure to gas.

Older adults may not use their gas cooking appliances as frequently as those living with small children. In a questionnaire survey of men and women aged 65 years or older in Bristol, United Kingdom, the presence of a gas hob or gas oven was associated with a small, non-significant risk of respiratory symptoms suggestive of COPD *(221)*. The risk of respiratory symptoms appeared to be higher in women than in men for gas hobs, although the gender interaction was not significant ($P > 0.05$). Many people in this age group will no longer be preparing meals for their families and no information was collected on the frequency of use of gas hobs and ovens. Associations may have been weak owing to infrequent cooking in this age group.

Many of the remaining cross-sectional studies in adults have been restricted to women. In Polish women over 65 years of age, chronic cough, chronic phlegm and shortness of breath on exertion were more common in those who cooked with gas for more than three hours a day compared to those who cooked with gas less frequently *(222)*. The authors reported that "decline in FEV_1" was also greater in this group, but this association was assessed by comparison of the age coefficient for regression equations of FEV_1 on height and age, stratified by those with short or medium/long daily exposure, and was not derived from repeated measurements of FEV_1 .

In a study of 1282 women in Singapore (223), there was a non-significant increased risk of respiratory symptoms among non-smoking women who cooked frequently and a significantly reduced adjusted FEV_1 noted in those who described themselves as housewives and who cooked frequently (0–2 times a week 1.82 litres; 3–14 times a week 1.62 litres; ≥ 15 times a week 1.61 litres). In Singapore, as in Poland, the use of gas for cooking was universal and greater exposure to "cooking with gas" also implies greater exposure to other substances generated by the cooking process. Stir frying with spices and chillies is a common method of cooking, and regular cooking is most likely to be associated with greater exposure to oil mists and frying fumes that may themselves cause respiratory symptoms. There was a strong association of chronic cough and phlegm with the frequency with which the kitchen was "filled with cooking fumes". This could

reflect poor ventilation and greater exposure to the products of gas combustion, but could also reflect greater exposure to pollutants created by cooking.

A cross-sectional study of asthmatics recruited into NHANES III *(215)* did not show an association of the use of gas cooking with asthma severity. Nearly half of the 445 asthmatics studied cooked with gas but they had only a non-significant increased prevalence of symptoms of wheeze and dyspnoea and had the same lung function (FEV_1, FVC or $FEF_{25–75}$) as those who cooked with electricity. The authors of this study concluded that their results "should be reassuring to adults with asthma and their health care providers". In another report, the same research group followed asthmatics living in California over an 18-month period. Those who cooked with gas had similar health service utilization rates (hospital admissions and emergency department visits) as those who cooked with electricity. There was no evidence that the reporting of use of a gas stove at baseline (or changing the use of that gas stove over the period of the follow-up) was associated with asthma severity or with SF-12 or asthma-specific quality of life scores, even though associations with exposure to ETS were observed *(224)*.

Health effects in adults: longitudinal studies looking at exposure to gas appliances. Longitudinal studies over several years of follow-up to examine the chronic respiratory health effects of gas cooking in adults are less common than cross-sectional studies, but some have been published. Keller et al. *(180)* examined incident lower respiratory illness in members of 441 families living in Ohio, United States by contacting the families every two weeks over a period of a year. About half of the families used electricity to cook and the rest used gas, but overall the rates of respiratory illness in mothers (and children) were lower in families with gas cookers than in families with electric cookers.

The longest follow-up has been of residents of households in Chesterfield, England, that were included in a housing survey in 1936. They were followed through the National Health Service Central Registry *(225)*. The presence of a gas cooker in the home at the time of the survey was not associated with overall mortality in children or adults and was negatively associated with death ascribed to COPD (RR 0.8; 95% CI 0.6–1.2). This result is unsurprising, as positive results would have implied a very strong association of gas cooking at one point early in life with development of severe respiratory disease many years later, without adjustment for smoking.

The largest longitudinal study with the most comprehensive analysis to examine respiratory outcomes in adults, based on exposures in earlier life, was from the 1958 birth cohort in the United Kingdom *(226)*. In a sample of 1500 adults enriched with people who had a history of wheezing in earlier assessments, information on the fuel currently used for cooking and the fuel used for cooking when the participant was 11 years old was collected at age 35 years. Of those who first reported symptoms indicative of asthma at the age of 7 years, those

who reported using gas for cooking at age 35 years were more likely to report current wheeze than those who currently used electricity for cooking (OR 1.26; 95% CI 0.84–1.88). This increased risk was greater in women (OR 1.82; 95% CI 1.02–3.26) than in men (OR 0.86; 95% CI 0.48–1.58) and in non-atopics (OR 1.84; 95% CI 1.05– 3.22) than in atopics (OR 0.76; 95% CI 0.39–1.49), but the interaction of gender and atopy with gas cooking for persistence of symptoms was not significant ($P > 0.05$). Cross-sectional analyses of the 243 people with asthma or wheeze in the previous year showed little evidence that the current use of gas for cooking was associated with current asthma severity as measured by number of attacks of asthma or the reporting of sleep disturbed by wheezing in the previous 12 months.

At variance with the results for symptoms is that decrements in lung function were associated with the use of gas for cooking in men (FEV_1 –141 ml; 95% CI –234 to –48 ml) but not in women, and current asthmatics showed worse lung function if they cooked with gas than if they cooked with electricity (FEV_1 –129 ml; 95% CI –234 to –14 ml). This latter association was not examined in men and women separately. The authors concluded that "past and current use of gas for cooking is unlikely to be a major influence on respiratory morbidity in young adults".

A longitudinal design was used to assess acute health effects of exposure to gas appliances in a panel study of 164 asthmatics living in Denver, United States *(227)*. Participants recorded symptoms, medication use and their use of indoor gas appliances. The reporting of moderate or severe cough and shortness of breath was associated with gas stove use on that day, the "non-users" comprising people with either a gas or an electric stove.

Studies conducted in developing countries

In developing countries, many people cook with either biomass or with gas (usually LPG). Use of biomass is associated with a range of health effects, which were reviewed in 2004 *(228)*. Solid fuel use was shown to be associated with acute lower respiratory tract infection, COPD, asthma, cataracts, tuberculosis and lung cancer. Association of nitrogen dioxide with disease in these settings is likely to be confounded by the high particulate counts. There has, however, been one study in Ethiopia where about 90% of homes cook with biomass (wood or charcoal) and the remainder cook with a modern fuel such as kerosene, gas or electricity *(229)*. Those who used kerosene had a significantly increased risk of IgE sensitization to aero-allergens, eczema and rhinitis compared to those who did not. Those who used gas had some increased risk and those who used electricity had an increased risk for eczema only. The authors argued that the increased risk of allergic outcomes in those using modern fuels producing nitrogen dioxide was unlikely to be explained by factors associated with socioeconomic status, as they had adjusted for this (family occupation, household crowding).

Health effects: type of gas

Some of the variation in the associations of gas cooking with symptoms may be explained by the type of gas used. In areas where there is no piped gas, LPG is often used. In a study of more than 25 000 children in the United Kingdom, there was no association of gas used for cooking or heating with wheeze symptoms *(230)*. Children who lived in homes that used bottled gas (which in this study also included paraffin) were at an increased risk of wheeze compared to those using electricity for heating (OR for speech-limiting wheeze 1.38). One of the few studies in developed countries to examine the association of bottled gas compared to mains gas on respiratory health in adults was conducted in Italy, where cooking with gas is almost universal. In a population-based study in the Po Delta *(231,232)*, 30% of people used bottled gas and 67% used natural gas for cooking. The type of gas used for cooking was closely associated with the type of heating in the home, and exposure status was defined by both heating and cooking appliances. The lowest prevalence of symptoms was in those with natural gas central heating and gas cooking. Dyspnoea was more common in men and women who used bottled gas for cooking compared to those who used natural gas. No effect modification by atopy was examined or reported. Viegi et al. *(231)* hypothesized that the use of bottled gas may produce more pollutants from gas combustion owing to inefficient burning that went unnoticed. Bottled gas appliances were not subject to the mandatory regulation and official inspection imposed on natural gas appliances.

Health effects: studies conducted in ice arenas

High concentrations of nitrogen dioxide are observed in indoor ice arenas that use resurfacing machines powered by combustion engines, and studies have been conducted to assess the effect of exposure to nitrogen dioxide in this setting. A review of studies in which measurements were made of both nitrogen dioxide and carbon monoxide in indoor ice arenas was published in 2002 *(233)*. Exposure to nitrogen dioxide in this setting is accompanied by exposure not only to carbon monoxide and particles but also to cold air, and cross-sectional studies suggesting a high prevalence of respiratory symptoms in ice hockey players and figure skaters *(234)* may reflect a response to cold air. This interpretation is supported by evidence that the prevalence of asthma is higher in those who participate in outdoor winter sports such as cross-country skiing *(235)*.

To overcome this problem, one study in Sweden compared respiratory symptoms in children who played ice hockey in ice arenas with propane-fuelled and electric resurfacing machines *(236)*. Some 1500 children aged between 10 and 16 years who had played ice hockey in the previous three years and had trained in one of 15 indoor ice arenas were identified. Nine of the arenas used a propane-fuelled resurfacing machine and the median nitrogen dioxide level obtained from three consecutive days of monitoring in each arena during opening hours was 190

μg/m^3, although there was considerable range in the daily measurements (28–1016 μg/m^3). The remaining six arenas used electric resurfacing and the equivalent indoor nitrogen dioxide levels were 9 μg/m^3 (4–31 μg/m^3). Symptom prevalence (wheezing in the last 12 months, exercise-induced wheeze, physician-diagnosed asthma or current rhinitis) was non-significantly higher in children who trained in arenas with an electric resurfacing unit rather than a propane unit. The authors then looked at children attending the propane arenas only. They considered exposure as "high nitrogen dioxide" if levels were above the median and low if below the median. All symptoms were more common in those attending high nitrogen dioxide propane arenas and this reached statistical significance for those who had ever had symptoms of rhinitis (OR 1.7; 95% CI 1.3–2.3), rhinitis in the last 12 months (OR 1.7; 95% CI 1.2–2.4) and those who had ever had wheezing (OR 1.4; 95% CI 1.0–1.9). The vast majority of the children (over 80%) had played ice hockey for more than three years in these arenas.

Chronic health effects of exposure were also examined in Finland *(43)*. Junior ice hockey players were asked to complete a questionnaire. Information on the weekly average nitrogen dioxide in the ice arenas in which they trained was collected (range 21–1176 μg/m^3; mean 228 μg/m^3). For each increase of 100 μg/m^3, the risk of reporting rhinitis and cough was significantly increased (OR 1.54; 95% CI 1.05–2.26 for rhinitis and OR 1.62; 95% CI 1.06–2.47 for cough) and that of mucus production and sore throat was non-significantly increased (OR 1.41; 95% CI 0.96–2.08 for mucus production and OR 1.43; 95% CI 0.88–2.35 for sore throat), although in the discussion the authors intimate that the relationship is non-linear.

There are case reports of acute pneumonitis in adult ice hockey players in the 24 hours after a match *(237,238)*, but these studies lacked indoor nitrogen dioxide measurements. However, as part of an investigation into acute onset of cough, haemoptysis and/or chest pain during or shortly after playing hockey in an indoor ice arena among the members of four ice hockey teams *(239)*, the mean nitrogen dioxide level during 30 minutes of resurfacing was found to be 7520 μg/m^3. In 1994, a similar incident occurred in Stockholm, Sweden, probably associated with exposures of up to 2358 μg/m^3 *(240)*, and five years later the prevalence of self-reported shortness of breath, wheezing, cough and rhinitis was higher in those exposed to the high levels of nitrogen dioxide than in the control group (ice hockey players who had trained in electric resurfacing arenas) *(241)*. Longer-term health effects of high-dose exposures were also reported from Philadephia, United States *(242)*. Six months after an incident in which 16 previously healthy hockey players developed symptoms following exposures thought to be between 658 and 2068 μg/m^3 for around 3 hours, 50% remained symptomatic. Impulse oscillometry tests before and after bronchodilator use suggested increased airway resistance and small airway disease in those reporting more symptoms.

Nitrous acid

Nitrous acid is present as a gas in indoor and outdoor air. In the indoor environment it is produced both directly by combustion processes, such as by the use of unvented gas appliances, and indirectly by absorption of nitrogen dioxide and then release of nitrous acid from water-containing surfaces in the home *(243)*. One chamber study in healthy volunteers showed that exercising in 650 ppb nitrous acid for three hours is followed by minor reductions in airway conductance *(244)* and another small study in asthmatics, again conducted in a chamber, showed that similar levels of exposure are associated with minor reductions in forced vital capacity *(245)*.

It has been established that the presence of nitrous acid will interfere with accurate measurement of nitrogen dioxide by most commonly used methods, and it has been proposed that adverse health outcomes that have been attributed to nitrogen dioxide (or to exposure to appliances producing nitrogen dioxide, such as gas stoves) could be confounded (or explained) by exposure to nitrous acid *(243,246)*. It has been argued that the variations in the reported association of indoor nitrogen dioxide with respiratory health may be explained by failure to measure this co-pollutant *(247)*. The dearth of studies in which both have been measured has been identified as a gap in our understanding of the health effects of gas appliances *(247)*.

In a study of infants at high risk of developing asthma because they had an older sibling with physician-diagnosed asthma, both indoor nitrous acid and nitrogen dioxide were measured and lung function assessed *(40)*. As referred to earlier in this chapter, the authors concluded that nitrogen dioxide, not nitrous acid, was more closely associated with lower lung function. Nevertheless, in a small study of British adults, decrements in lung function were associated with exposure to nitrous acid in the kitchen (predicted decrease in FEV_1 0.96% (95% CI 0.09–1.82) and decrease in FEV_1/FVC 0.45% (95% CI 0.06–0.83) per 1-ppb increase in indoor nitrous acid) and the association persisted after adjustment for nitrogen dioxide *(248)*.

Health risk evaluation

The main health outcomes of interest are respiratory symptoms, bronchoconstriction, increased bronchial reactivity, airway inflammation, and decreases in immune defence leading to increased susceptibility to respiratory infection. No other health effects have been consistently associated with exposure to nitrogen dioxide in the indoor environment.

Quality of exposure and effect assessment

Controlled exposure studies in humans that assess the health effects of short-term exposures give no cause for concern regarding exposure assignment/measurement. In epidemiological studies, exposure assignment is less precise, being

based on passive samplers (which provide average levels over several hours or weeks) or on proxy measurements (e.g. the presence of a gas appliance). The latter is an imprecise estimate of actual exposure but, at group level, is associated with elevated long-term indoor exposure to nitrogen dioxide and with short-term peaks of exposure. No biomarker is available.

Controlled exposure studies in humans assessing the health effects of short-term exposures have used well-standardized, objective methods for the assessment of health effects. In epidemiological studies, self- (or maternally) reported symptoms have been widely used as the health metric. These measurements are susceptible to over-reporting by those who perceive their exposure to be high. Although lung function measures provide more objective estimates of health status, inflammatory changes and symptoms may occur in the absence of lung function changes.

Controlled exposure studies in humans have shown acute respiratory health effects of short-term exposures in healthy volunteers or those with mild pre-existing lung disease. Mechanical failure of resurfacing machines in ice arenas leading to short-term, high-dose exposures demonstrates similar effects and suggests there may be long-term sequelae. Population-based studies have shown health effects of chronic indoor nitrogen dioxide exposure in infants, children and adults.

Levels and duration of exposure

Controlled exposure studies in humans have assessed acute health effects to short-term exposure (maximum of several hours) at levels consistent with peak exposures experienced when gas appliances are used, but well above the average levels in most indoor environments. The majority of epidemiological studies have examined populations with average indoor levels that can be considered representative of longer-term population exposures.

Exposure–response relationship

There is evidence of a dose–response effect in controlled exposure studies (particularly at high levels) and in epidemiological studies. There is no evidence for a threshold in epidemiological studies. The exposure–response effect of repeated daily peak exposures to nitrogen dioxide is not known.

Susceptible population or response modifiers to consider in guideline setting

Controlled exposure studies assessing the health effects of short-term exposures show health effects at lower levels more consistently in asthmatics than in non-asthmatics, and both chamber studies and some epidemiological studies suggest that exposure enhances the response to allergens in those who are sensitized. Some epidemiological studies suggest stronger associations of respiratory health

with indoor nitrogen dioxide in females compared to males, but it is not clear whether this is due to women spending more time indoors or an underlying biological basis.

Quality of evidence

Although associations of exposure with health are well-documented, there is unexplained heterogeneity in results from well-conducted studies. This may reflect underlying variations in the nature of the exposure or in host susceptibility.

There is sufficient evidence of a causal relationship between controlled exposure to nitrogen dioxide concentrations as low as 380–560 μg/m^3 for periods of one hour or longer and a range of responses within the lung that suggest airway inflammation and alteration in lung immune defences in asthmatics. Recent systematic review and meta-analysis provides suggestive evidence that controlled exposures to as low as 188–360 μg/m^3 are associated with small increases in airway reactivity to a range of stimuli in asthmatics. Studies that have examined health effects of repeated short exposures to 500 μg/m^3 provide suggestive evidence that this is associated with exaggerated/prolonged response to allergen challenge in asthmatics/atopics. There is limited or suggestive evidence of an association between indoor nitrogen dioxide at levels currently occurring in populations and (*a*) reported respiratory symptoms in children, (*b*) increased reporting of symptoms in children with asthma, (*c*) increased asthma severity following respiratory viral infection and (*d*) reported respiratory symptoms in adults.

Health relevance of current indoor exposures in various regions of the world

Epidemiological studies conducted in several countries show that a proportion of homes and classrooms have indoor nitrogen dioxide levels exceeding the WHO ambient guidelines for outdoor air.

Indoor studies suggest that those using gas cookers, particularly in poorly ventilated spaces, can experience peak nitrogen dioxide exposures in excess of 500 μg/m^3. Important factors that may increase indoor exposure are the use of unvented gas appliances, poor ventilation, proximity to major highways and the use of propane- and petrol-fuelled ice resurfacing machines in indoor ice arenas.

Guidelines

A 1-hour indoor nitrogen dioxide guideline of 200 μg/m^3, consistent with the existing WHO air quality guideline, is recommended.

At about twice this level, asthmatics exhibit small pulmonary function decrements. Those who are sensitized may have small changes in airway responsiveness to a variety of stimuli already at this level. Studies of the indoor environment provide no evidence for an indoor guideline different to the ambient guideline.

An annual average indoor nitrogen dioxide guideline of 40 μg/m^3, consistent with the existing WHO air quality guideline, is recommended.

The ambient annual average guideline of 40 μg/m^3 was initially based on a meta-analysis of indoor studies. It was assumed that having a gas stove was equivalent to an increased average indoor level of 28 μg/m^3 compared to homes with electric stoves, and the meta-analysis showed that an increase in indoor nitrogen dioxide of 28 μg/m^3 was associated with a 20% increased risk of lower respiratory illness in children. Homes with no indoor sources were estimated to have an average level of 15 μg/m^3. Several exhaustive reviews to further develop ambient guidelines have not challenged these findings.

Recent well-conducted epidemiological studies that have used measured indoor nitrogen dioxide levels support the occurrence of respiratory health effects at the level of the guideline.

The guidelines section was formulated and agreed by the working group meeting in November 2009.

Summary of main evidence and decision-making in guideline formulation

Critical outcome(s) for guideline definition

Respiratory symptoms, bronchoconstriction, increased bronchial reactivity, airway inflammation and decreases in immune defence, leading to increased susceptibility to respiratory infection.

Source of exposure–effect evidence

- Short-term exposures: human controlled exposure experimental studies indicating minor changes in pulmonary function in people with asthma exposed to 560 μg/m^3 nitrogen dioxide for up to 2½ hours *(124–126)*. Small increases in airway reactivity to a range of stimuli in asthmatics at repeated short exposures to 500 μg/m^3 *(131,133,136,137)*.
- Long-term exposures: meta-analysis of studies on association of lower respiratory illness in children showing that an increase in indoor nitrogen dioxide of 28 μg/m^3 above the background of ca. 15 μg/m^3 was associated with a 20% increased risk of lower respiratory illness in children *(170)*.

Supporting evidence

- Significant association of various respiratory symptoms or lung function indices with nitrogen dioxide measured indoors or as personal exposure in all identified epidemiological studies of asthmatics *(23,26,160–162,164,165,168,191,268)*. Lowest measured levels were ca. 5 μg/m^3.
- Associations also found in half of the studies of non-asthmatic children *(10,27,40,146,147,148,153,154,156,158,208)*.

Results of other reviews

WHO *Air quality guidelines: global update 2005 (15)* and EC INDEX project *(5)* agreed on the same set of guidelines.

Guidelines

- 200 μg/m^3 – 1 hour average.
- 40 μg/m^3 – annual average.

Comments

No evidence from epidemiological studies for an exposure threshold.

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Table 5.1. Levels of nitrogen dioxide in various countries

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
Baxter et al. *(24,25)*		United States (Boston, MA)	3–4 days from 2003 to 2005 in 2 seasons (May–October, December–March)	
Belanger et al. *(164)*		United States	Palmes tubes	
Berglund et al. *(249)*	INDEX	Sweden	24 hours Urban area Rural area	Schoolchildren, personal exposure
Bernard et al. *(250)*		France	14 days (passive monitors)	
Blondeau et al. *(21)*	PRIMEQUAL	France (La Rochelle)	2 weeks	
Brauer et al. *(251)*	International survey NO_2 indoor ice skating	9 countries	1 week average	
Breysse et al. *(252)*		United States (Baltimore, MD)	72 hours	
Chao *(253)*		China (Hong Kong SAR)		
Cyrys et al. *(254)*	THADE	Germany (Hamburg) Germany (Erfurt)	1 week mean	Living room
Diette et al. *(163)*		United States (East Baltimore, MD)	72 hours	Bedroom
Dutton et al. *(33)*		United States (Boulder, CO)	4 hours in 1999	
Emenius et al. *(143)*	BAMSE birth cohort	Sweden (northwest Stockholm): Urban area Semi-urban area Suburban area	4 weeks (passive samplers)	Living room
Franklin et al. *(37)*		Australia	During summer (passive samplers)	Kitchen

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
	43	37.5 (mean)	Low socioeconomic status households (I/O ratio 0.99 +/– 0.63)
Electric stoves	728 children	16.45 (SD 17.41)	
Gas stoves		49.55 (SD 34.62)	
		13 (median) 7 (median)	Most important source of exposure = indoor ice skating (levels up to 8000 $\mu g/m^3$)
	107 volunteers	31.9 (mean) / 12.7 (SD)	Personal exposure
	8 schools		I/O ratio 0.88–1
Type of fuel used in the resurfacing machine	332 ice arenas	436.16 (AM) (breathing height to the ice surface); 422.77 (spectators' area)	
	100 (bedroom)	60.45 / 76.9 (SD)	25% of the samples below the limit of detection
	60 people (personal exposure)	46 (mean) (60 personal exposures)	When cooking 59.7 $\mu g/m^3$; when not cooking 41.8 $\mu g/m^3$
	12 people (homes: living room, bedroom, kitchen)	47.3 (mean) (12 personal exposures; 55.2 (12 indoor measurements)	
	201	17 (median)	
	204	15 (median)	
	300 Inner-city preschool children (150 with asthma, 150 controls)	41.32 (median, children with asthma); 40 (median, controls)	
	2	688.68 (mean)	Measurements during operation of unvented natural gas fireplaces
Few gas combustion appliances	540		Mean outdoor levels:
(8.52% of homes with gas stove)		18.3 (mean) (8 – 45.1) 12.2 (mean) (4.4 – 25.1) 8.1 (mean) (2.3 – 21.1)	31.5 (17.9–46.7) 21.6 (8.7–36.4) 13.7 (6–29)
Gas cooker	53	Average 16.2 (12.7–20.6); peak 45.3 (36–57.1)	

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
Gallelli et al. *(255)*	THADE	Italy (Genoa)	2 months in 2000 (passive diffusion tubes)	Kitchen Bedroom
Garcia Algar et al. *(256)*		United Kingdom (Ashford) Spain (Menorca) Spain (Barcelona)	Between 7 & 15 days (passive filter badges)	
Garcia Algar et al. *(13)*		Spain (Barcelona)	Over 7–30 days between 1996 & 1999 (passive filter badges)	
Garrett et al. *(31)*	THADE	Australia (Latrobe Valley, Victoria)	4 days in 1994/1995 (passive samplers)	
Gee et al. *(257)*	THADE	United Kingdom (Manchester)	5 days	Living room Bedroom
Gilbert et al. *(258)*		Canada (Quebec City)	7 days between January & April 2005 (passive monitors)	
Guo et al. *(259)*	INDEX	China (Hong Kong SAR)	15 minutes 15 minutes	Ice skating arenas
Hagenbjork-Gustafsson et al. *(7)*	THADE PEACE	Sweden (Umeå, suburban control)	2 x 24 hours between January & March 1994	
Hazenkamp-von Arx et al. *(16)*	ECRHS II	21 European study centres of ECRHSII (from northern Italy to Iceland)	14 days in 2000 (passive sampler)	
Kattan et al. *(23)*	NCICAS	United States (8 inner city areas)	7 days (Palmes tubes)	Child's sleeping area

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
	89	47 (indoor mean) 24.78 (indoor mean) 24.9 +/– 7.8 (students, personal exposure); 44.3 +/–10.1 (workers); 40 +/– 13.4 (housewives)	
Gas combustion appliances, cigarette smoking	1421 (living room wall)	11.07 (median) 11.59 (median) 45.66 (median)	
	340	45 (mean in 1996); 53.22 (mean in 1997); 51.69 (mean in 1999)	
Gas stoves, vented gas heaters, smoking	80	11.6 (median, ranging from < 0.7 to 246)	Highest levels recorded in winter
	69	27.2 (AM) 20.3 (AM)	
	96	8.3 (3.3–29.1)	
Gasoline fuelled Propane fuelled		58 – 91 (AM) 242 (AM)	
No gas appliances	23 (urban area) 20 (suburban control area)	11 (mean in urban area) 6 (mean in control area)	I/O ratio: 0.44 I/O ratio: 0.67 Heavier traffic density in Umeå
		Annual mean from 4.9 to 72.1	
Gas stoves	469 (1444 children)	57 (median)	Indoor levels considerably higher than US national outdoor median value (34.43)

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
Kousa et al. *(260)*	EXPOLIS	Switzerland (Basel) Finland (Helsinki) Czech Republic (Prague)	48 hours in 1996/1997 (passive samplers)	
Lambert et al. *(11)*	THADE	United States (Albuquerque, NM)	2 weeks mean in 1988–1991 (passive diffusion samplers)	Kitchen Living room Bedroom
Lawrence et al. *(30)*		India (Agra)	October 2002 to February 2003 (multigas monitor)	
Lee & Wang *(41)*	INDEX			Chamber test
Lee et al. *(39)*		United States (2 communities: Upland & San Bernardino County, southern California)	6 days in April & May 1996 (passive samplers)	
Leung et al. *(9)*	THADE	China (Hong Kong SAR)	1 week mean (stationary samplers)	Kitchen Bedroom Lounge
Levy et al. *(3)*	THADE	Finland (Kuopio) Norway (Kjeller) Switzerland (Geneva) Germany 1 (Erfurt) Canada (Ottawa) Germany 2 (Berlin) Croatia (Zagreb) United States (Boston, MA) United Kingdom 3 (London) Japan 2 (Sapporo) Philippines (Manila) China (Beijing) Poland (Sosnowiec) Republic of Korea 1 (Taejon) India (Bombay)	48 hours in 1996	

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
	262 adults	27/13 (SD in residential indoor) to 36/24 (SD in workplace) 18/11 (SD in residential indoor) to 27/15 (SD in workplace) 43/23 (SD in residential indoor) to 30/18 (SD in workplace)	Mean outdoor levels: 36 +/– 13 24 +/– 12 61 +/– 20
Gas cooking stoves	1205 children / homes	65.04 (AM) 55.48 (AM) 40.17 (AM)	Lower indoor concentration observed during the summer
		487.81/279.3 (SD)	Measurements conducted in rural, urban and roadside
Mosquito coils and candles burning		17–91 (AM)	NO_x most abundant gas pollutants relating to candle burning
	119 homes (57 in Upland, 62 in San Bernardino)	53.56 (mean)	Average indoor NO_2 concentration (38.26 $\mu g/m^3$) was significantly higher than outdoor concentrations
	40 homes	93.16 (AM) 58.1 (AM) 59.6 (AM)	
	30 30 33	10.34 (mean) 14.66 (mean) 15.60 (mean)	
	29 29 31 15 20	16.97 (mean) 20.12 (mean) 23.12 (mean) 31.58 (mean) 36.10 (mean)	
	117	40.42 (mean)	
	59 14	43.43 (mean) 45.12 (mean)	
	44 15	47.75 (mean) 64.67 (mean)	
	40	72.76 (mean)	
	20	76.70 (mean)	

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
		Japan 3 (Tokushima) Republic of Korea 2 (Seoul) Mexico (Mexico City)		
Lindgren *(261)*				Cabins
Mi et al. *(262)*		China (Shanghai)	7 days (diffusion samplers)	30 classrooms
Monn et al. *(263)*	THADE SAPALDIA	Switzerland (4 urban, 2 rural & 2 alpine areas)	1 week in 1993/1994 (passive sampler)	Personal exposure
Mosqueron et al. *(264)*		France (Paris)	48 hours (passive samplers)	Personal exposure Living room Indoor office
Nakai et al. *(18)*		Japan (Tokyo)	10 seasons over 3 years (personal exposure)	
Noy et al. *(265)*	INDEX	Netherlands	3 measurements of 1 week within a year (Palmes tubes)	Kitchen
Osman et al. *(187)*		United Kingdom(North East Scotland)	1 week	Living room
Pennanen et al. *(42)*	INDEX	Finland	Max 15 minutes Max 1 hour	Indoor ice arenas
Pennanen et al. *(266)*	INDEX	Finland	1 week	

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
	30	78.77 (mean)	
	31	81.22 (mean)	
	30	117.88 (mean)	
	26; intercontinental flights (Boeing 767-300)	14.1 (mean) 37 (max)	
	10 naturally ventilated schools	33–85	Outdoor : 45 – 80 $\mu g/m^3$ I/O ratio : 0.63 – 1
Gas cooking Smoking	more than 500 subjects	27 (average personal exposure) 21 (average indoor measurements)	Personal exposure correlated best with indoor; outdoor average 31 $\mu g/m^3$
	62 office workers	43.6 (mean personal exposure) 35.1 (mean in home) 44.9 (mean in office)	
Gas cooking stoves, heaters	50 residents from 3 residential zones A: 0–20 m from the roadside B: 20–150 m from the roadside C: residential district, suburban area	 121.28 (mean) 116.7 (mean) 105.79 (mean)	Outdoor concentrations in zone A were always the greatest
Gas stoves		2500 (max)	
Smoking (39% of the 148 patients)	148 patients (home measurements)	14.92 (mean)	
Ice resurfacing machines with combustion engines		320 – 7530 (max) 270 – 7440 (max)	Highest levels with propane-fuelled ice resurfacing machines and insufficient ventilation
Ice resurfacing machine: propane petrol electric	69 Indoor ice arenas	2–1838 396 (AM) 283 (AM) 25 (AM)	

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
Piechocki-Minguy et al. *(267)*		France	2–24-hour sampling periods (1 during a working day, 1 during the weekend) (personal measurements, diffusion samplers)	4 categories of microenvironment
Pilotto et al. *(27)*		Australia	Hourly peak level (personal exposure)	
Pilotto et al. *(268)*		Australia	9 days (classrooms) 3 days (each household)	Classrooms Dwellings
Ponzio et al. (269)	ECRHS II	Italy (Pavia)	2001–2002	
Raw et al. *(270)*	National representative survey	England	2 weeks in 1997–1999 (Palmes tubes)	Kitchen Bedroom
Riedeker et al. *(271)*		United States (California)	25 work shifts (3 p.m. to midnight) in autumn 2001	
Ross *(272)*		United Kingdom	7-day average and maximum 1-hour average (Palmes samplers)	12 homes
Sabin et al. *(273)*		United States (Los Angeles, CA)	24 morning and afternoon commutes & 10 additional runs	
Saintot et al. *(274)*	THADE SUVIMAX	France	2 periods of 5 consecutive days (1 in winter, 1 in autumn of 1998)	
Sakai et al. *(275)*	INDEX	Sweden (Uppsala) Japan (Nagoya)	24 hours in February through May 1998, 24 hours in February 1998 (diffusion sampler)	Urban dwellings Urban dwellings
Salonen et al. *(43)*			Personal exposure	

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
		From 17 on summer weekend to 38 on winter weekday	Indoor environments contributed more than 78% to total personal exposure
Unflued gas appliances at home	41 classrooms (388 children)	153 (max)	
Unflued gas heating	10 control schools (unflued gas heating) 8 intervention schools (replacement flued gas or electric heaters installed)	89.91/51.26 (SD, control schools) 29.65/12.62 (SD, intervention schools)	
	114	47.1/24.5 (SD)	
	845 homes	21.8 (GM) 11.9 (GM)	
	Patrol cars	41.7 (mean)	
Kitchen, living room, bedroom		191–1148 (hourly mean)	
	Conventional diesel school buses	64–220; 370 (max)	
	294	43/26.1 (SD) in winter 43.8/20.6 (SD) in autumn	
	27 37	6.7 (GM); 11 (max) 98 (GM); 369 (max)	
Ice resurfacing machines	793 young ice hockey players	21–1176	

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Reference	Project / programme	Country	Averaging time / survey year(s) / methods	Location of measurement
Shima et al. *(10)*	THADE	Japan (Chiba)	24-hour mean (2 × 24 hours, 1 in January or February 1993, 1 in June or July 1993 (passive samplers)	
Simoni et al. *(12)*	INDEX	Italy (Po Delta)	2 weeks (1 in winter, 1 in summer)	
Simoni et al. *(188)*	THADE	Italy (Pisa, urban) Italy (Po Delta, rural)	1 week (summer or winter) in 1991–1994	
Son et al. *(276)*	THADE	Korea (Asan & Chuna)	Passive samplers; house measurements & personal exposure	
Thunqvist et al. *(236)*		Sweden	3 consecutive days (passive diffusion samplers)	
Yang et al. *(46)*		Australia (Brisbane) Republic of Korea (Seoul)	30 consecutive days 21 consecutive days (passive filter badges)	
Zhao et al. *(277)*		China (Taiyuan)		
Zipprich et al. *(278)*		United States (Richmond, VA)	48 hours (personal exposure & indoor concentrations, July to September, passive samplers)	
Zmirou et al. *(279)*		France (Paris, Nice, Toulouse, Clermont-Ferrand, Grenoble)	48 hours (personal exposure & indoor measurements) between 1998 and 2000	Personal exposure & indoor measurements
Zota et al. *(32)*		United States (Boston, MA)	Palmes tubes	Kitchen Living room

Emission source	Number of homes / volunteers	NO_2 measurement results ($\mu g/m^3$) [a]	Comments
	842 schoolchildren	Homes with vented heaters 35.2 (mean) in winter; homes with unvented heaters 32 (mean) in winter	Concentrations in winter very much higher in homes with unvented heaters than in those with vented heaters
	383 adults (homes)	38.26 (median in winter); 26.78 (median in summer); 63.13 (kitchen in winter); 38.26 (kitchen in summer)	
	282 139	28.7 (mean) 42.09 (mean)	
	31 taxi drivers (houses)	47.25 /20.47 (SD in houses); 57.96 /18.56 (SD personal exposure)	Personal exposure more strongly correlated with interior of vehicle
Combustion engine-powered resurfacing machine	9 propane machines 6 electric machines	276 (28–015) 11 (2–30)	
	28 houses 37 houses	15.8 / 18.2 (SD) 44.7 / 38.1 (SD)	I/O ratio 0.88 +/– 0.32
	10 schools	39.4 (mean)	Outdoor levels were 2–3 times higher
	39 adults 9 children in 23 households	30.6 (personal exposure) 24.87 (personal exposure) 34.43 (bedrooms) 36.34 (living rooms)	
	217 pairs of matched 4–14-year-old cases & controls	36.1/21.4 (SD, indoor concentrations); 31.4/13.9 (SD, personal exposure)	Indoor levels higher in the heating season
Gas stove use Reduced air exchange rate during the heating season	77 homes	82.26/38.26 (SD) 68.87/32.52 (SD)	

[a] AM = arithmetic mean, SD = standard deviation, GM = geometric mean, max = maximum value.

Table 5.2. Studies that have examined associations between respiratory symptoms and indoor measurements of or personal exposure to nitrogen dioxide

Reference	Participants	NO_2 exposures in the study
Florey et al. *(148)*	Children	One week mean bedroom (mean): electric cooker 5.64–69.6 µg/m^3; gas cooker 7.52–317.7 µg/m^3
Hoek et al. *(151)*	Children aged 6 years	One-week average (range): kitchen 110–789 µg/m^3; living room 17–277 µg/m^3; bedroom 10–146 µg/m^3
Dijkstra et al. *(150)*	Children aged 6–12 years	Given in Fig. 2 of paper
Koo et al. *(155)*	Children aged 7–13 years	24-hour personal mean: children: 35.9 µg/m^3; mothers: 36.5 µg/m^3
Neas et al. *(153)* (supported by Li et al. *(154)*)	Children aged 7–11 years	Household annual average: without an NO_2 source 16.1 µg/m^3; with an NO_2 source 44.2 µg/m^3
Infante-Rivard et al. *(156)*	Children aged 3–4 years	24-hour personal average: without an NO_2 source 17.3 µg/m^3; with an NO_2 source 32.3 µg/m^3
Samet et al. *(140)*	Infants	Two-week average bedroom: 22% of measures greater than 37.6 µg/m^3
Pilotto et al. *(27)*	Children aged 6–11 years	Winter six-hour average in classrooms: electrically heated, range 13.2–43.2 µg/m^3; gas heated, range 33.8–248.2 µg/m^3
Garret et al. *(152)*	Children aged 7–14 years	Bedroom, living room and kitchen: "indoor" median 11.6 µg/m^3 (5.01–27.9 as 10th & 90th centiles)

Results
Prevalence of respiratory illness: 0–37.6 μg/m^3, 44%; 37.6–75.2 μg/m^3, 59%; > 75.2 μg/m^3, 71%; *P* for trend < 0.05
No association of levels in any of the three locations with symptoms
Odds ratio of symptoms comparing > 60 μg/m^3 Cough 0.80 (0.21–3.05) Wheeze 0.94 (0.37–2.40) Asthma 0.56 (0.15–2.06) No association with lung growth
Unadjusted comparison of mean levels in those with and without symptoms: cough *P* = 0.99 children; asthma *P* = 0.42 children; allergic rhinitis *P* = 0.75 children
Cumulative incidence of respiratory illness: adjusted OR 1.4 (1.14–1.72) per 28.2 μg/m^3
Adjusted OR for asthma: not detectable, 1.00; <18.8 μg/m^3, 0.95 (0.31–2.95); 18.8–28.2 μg/m^3, 3.85 (0.92–16.09); ≥ 28.2 μg/m^3 19.87(4.75–83.03)
No association
Adjusted difference in mean symptom rates for high (≥ 75.2 μg/m^3) compared to low (<75.2 μg/m^3): Sore throat *P* = 0.03 Cough with phlegm *P* = 0.06 Dry cough *P* = 0.9 Wheeze *P* = 0.2 Absent from school *P* = 0.01 Adjusted OR for having at least one day with symptom for high (≥ 75.2 μg/m^3) compared to low (< 75.2 μg/m^3): Sore throat 1.39 (0.80–2.41) Cough with phlegm 1.28 (0.76–2.5) Dry cough 1.08 (0.62–1.90) Wheeze 1.41 (0.63–3.15) Absent from school 1.92 (1.13–3.25)
Adjusted OR per 10 μg/m^3: Cough 1.47 (0.99–2.18) Wheeze 1.15 (0.85–1.54) Asthma attacks 1.06 (0.77–1.46)

Reference	Participants	NO_2 exposures in the study
Magnus et al. *(142)*	Infants from birth to 2 years	Mean living room level 14.7 μg/m^3 (2–43 μg/m^3)
Mukala et al. *(158)*	Pre-school children	Study median 21.1 μg/m^3
Shima et al. *(10)*	Children aged 9–10 years	Mean annual living room: Vented appliances 34.5 μg/m^3 Unvented appliances 60.9 μg/m^3 Winter mean: Vented appliances 45.1 μg/m^3 Unvented appliances 141.1 μg/m^3
Ponsonby et al. *(208)*	Primary school children	Mean personal exposure 19.0 μg/m^3
Emenius et al. *(143)*	Children from birth to 2 years	Mean living room: Urban, no gas stove 16.4 μg/m^3 Urban, gas stove 22.6 μg/m^3 Semi-urban 12.2 μg/m^3 Suburban 8.1 μg/m^3
Belanger et al. *(147)*	Infants who had a sibling with asthma	Two-week mean living area: interquartile range 9.6–32.7 μg/m^3
van Strien et al. *(40)*	Infants from birth to 1 year who had a sibling with asthma	Two-week mean living area: interquartile range 9.6–32.7 μg/m^3
Sunyer et al. *(145)*	Infants	Median in each of three centres: 10.7, 22.2 & 86.2 μg/m^3
Diette et al. *(163)*	Children aged 2–6 years	
Raaschou-Nielsen et al. *(144)*	Infants from birth to 18 months	Mean ten-week average bedroom 8.6 μg/m^3 (95% range 3.3–17.6 μg/m^3)

Results
No association with symptoms of bronchial obstruction and physical signs as identified by physician
Adjusted risk ratio of reporting cough during the same week as measurement: < 16.2 μg/m^3, 1.00; 16.2–27.2 μg/m^3, 1.23 (0.89–1.70); ≥ 27.2 μg/m^3, 1.52 (1.00–2.31) *Adjusted for allergy, stove type, smoking, parental education, day care centre, season*
Adjusted OR per 18.8 μg/m^3 increase: *Boys* Wheeze 0.98 (0.68–1.39) Asthma 0.77 (0.48–1.20) *Girls* Wheeze 1.90 (1.30–2.83) Asthma 1.63 (1.06–2.54)
No association with incidence of wheeze or asthma over 3-year period Difference in post-cold-air challenge FEV_1/FVC ratio per 1.88 μg/m^3: –0.12 (–023 to –0.01) *Adjusted for height, sex, technician, smoking exposure, days between NO_2 measurements, spirometry*
Recurrent wheezing: < 8.4 μg/m^3, 1.00; 8.4–11.7 μg/m^3, 0.97 (0.42–2.24); 11.7–15.6 μg/m^3, 1.17 (0.46–2.99); > 15.6 μg/m^3, 1.48 (0.91–2.42) *Adjusted for gender, family history of asthma, smoking, breastfeeding, age of building*
Persistent cough per 18.8 μg/m^3 increase in living room NO_2: 1.21 (1.05–1.40) *NB: most of the pertinent data from this study presented in paper by van Strien (40)*
Adjusted relative rate of symptoms (1st, 2nd, 3rd, 4th quartiles of NO_2): Wheeze 1.00; 1.15 (0.79–1.67); 1.03 (0.69–1.53); 1.45 (0.92–2.27) Persistent cough 1.00; 0.96 (0.69–1.36); 1.33 (0.94–1.88); 1.52 (1.00–2.31) Shortness of breath 1.00; 1.59 (0.96–2.62); 1.95 (1.17–3.27); 2.38 (1.31–4.34) *Quartile cut-offs for analyses 5.1, 9.9, 17.4 μg/m^3* *Adjusted for season, parental asthma, mother's ethnicity, mother's education, smoking in the home, day care, living in an apartment, presence of siblings, gender, nitrous acid*
Adjusted OR for lower respiratory tract illness: < 9.4 μg/m^3, 1.00; 9.4–18.8 μg/m^3, 0.88 (0.63–1.23); 18.8–56.4 μg/m^3, 0.99 (0.69–1.43); ≥ 56.4 μg/m^3, 1.31 (0.75–2.26)
Median (IQR) three-day bedroom NO_2 (μg/m^3): children without asthma, 39.3 (26.3–58.3); children with asthma, 40.6 (26.3–63.9); $P = 0.84$
Adjusted odds of wheezing in first 18 months: < 5.2 μg/m^3, 1.00; 5.2–6.8 μg/m^3, 0.66 (0.27–1.61); 6.8–8.6 μg/m^3, 0.80 (0.32–2.01); 8.6–11.7 μg/m^3, 1.15 (0.40–3.32); ≥ 17.7 μg/m^3, 0.43 (0.15–1.18) *Adjusted for sex, area, mother's education, lung function*

Reference	Participants	NO_2 exposures in the study
Morales et al. *(146)*	Children aged 4 years	Median two-week average living room 21.6 µg/m^3; range 0.8–185.9 µg/m^3
Adults		
Keller et al. *(180,181)*	Adults	Mean 24-hour average. cooking with electricity 37.6 µg/m^3 ; cooking with gas 94.0 µg/m^3
Fischer et al. *(185)*	Women aged 40–60 years	Weekly mean: kitchen 18.8 –735 µg/m^3 ; living room 15.1–372.4 µg/m^3 ; bedroom 15.1–99.6 µg/m^3
Koo et al. *(155)*	Mothers	Personal NO_2: user of LPG/kerosene (no fan) 37.7 µg/m^3; user of LPG/ kerosene (fan) 41.7 µg/m^3
Simoni et al. *(188)*	Population-based sample	Seven-day mean indoor (average of kitchen, bedroom and living room): Pisa summer 24.4 µg/m^3; Po Delta summer 28.2 µg/m^3; Pisa winter 28.2 µg/m^3; Po Delta winter 41.4 µg/m^3
Triche et al. *(186)*	Mothers	Two-week average No source: median 25.3 µg/m^3; max 276 µg/m^3; source: median 22.7 µg/m^3; max 312.8 µg/m^3
Studies in asthmatics		
Smith et al. *(160)*	Asthmatics (children and adults)	Personal indoor daily mean 6.9–275.6 µg/m^3
Chauhan et al. *(165)*	Asthmatics	Geometric mean personal exposure 10.6 µg/m^3
Pilotto et al. *(268)*	Children with asthma (randomized controlled trial)	Six-hourly average levels: intervention classes 13.2–71.4 µg/m^3; non-intervention classes 22.5–218.1 µg/m^3

Results
Change in cognitive function score (95% CI) per 1.88-μg/m^3 increase; GSTP genotype: Ile/Ile 0.10 (– 0.22 to 0.42); Ile/Val or Val/Val –0.55 (– 0.86 to –0.25); *P* for interaction = 0.04 Adjusted OR (95% CI) of inattention symptoms; GSTP genotype: Ile/Ile 0.98 (0.88–1.09); Ile/Val or Val/Val 1.11 (1.03–1.20); *P* for interaction = 0.26 *Adjusted for maternal social class, maternal education, school age, observer, maternal smoking in pregnancy, number of smokers in home, maternal alcohol consumption during pregnancy, home location*
No association with respiratory illness observed
Adjusted difference in annual decline in FEV_1 (se) per unit change in NO_2: kitchen –0.025 ml (0.021); living room –0.048 ml (0.043); bedroom –0.164 ml (0.165)
Personal exposure level Without chronic cough 35.9 μg/m^3; with chronic cough 42.3 μg/m^3; *P* = 0.05 Without allergic rhinitis 35.5 μg/m^3 ; with allergic rhinitis 42.4 μg/m^3; *P* = 0.002
Generated personal exposure as product of hours per day indoors and measured indoor levels Divided exposure into two categories (above and below the median) Adjusted OR for acute respiratory symptoms with fever (high vs low): 1.66, 95% CI 1.08–2.57 No association with asthma/bronchitic symptoms without fever, or with peak flow, or with irritant symptoms, or with non-specific symptoms (values not given) *Adjusted for sex, age, active smoking and area of residence*
Adjusted OR of symptom comparing > 150.4 μg/m^3 with other measures: wheeze 4.00 (1.45–11.0); chest tightness 1.94 (0.98–3.85)
Adjusted OR in under 14-year-olds: wheeze 1.04 (0.89–1.12); cough 1.07 (0.89–1.29); daytime attacks of asthma 1.13 (1.02–1.26) No associations seen in other age groups
Risk of asthma exacerbation following infection
Mean rate ratio (intervention vs control) Difficulty breathing in day 0.41 (0.07 –0.98) Difficulty breathing at night 0.32 (0.14–0.69) Chest tightness 0.45 (0.25–0.81) Asthma attacks during the day 0.39 (0.17–0.93)

Reference	Participants	NO_2 exposures in the study
Nitschke et al. *(168)*	Children with asthma aged 5–13 years	Indoor daily mean (range): classrooms 16.9–577.2 μg/m^3; kitchens 5.6–795.4 μg/m^3
Belanger et al. *(164)*	Children with asthma aged < 12 years	Median average 10-day living room: homes without a source 16.2 μg/m^3; homes with a source 48.7 μg/m^3 Mean average 10-day living room: single-family homes 19.2 μg/m^3; multi-family housing 43.1 μg/m^3
Delfino et al. *(161)*	Children with asthma aged 9–18 years	Personal exposure: range 5.1–198.7 μg/m^3
Delfino et al. *(162)*	Children with asthma aged 9–18 years	Personal exposure: range 5.1–198.7 μg/m^3
Kattan et al. *(23)*	Children with asthma aged 4–9 years	Bedroom: median 56.0 μg/m^3 (0.9–902.4 μg/m^3)
Hansel et al. *(26)*	Children with asthma aged 2–6 years (same asthmatic children as included in Diette et al. *(163)*)	Mean three-day average bedroom: without gas stove 31.6 μg/m^3; with gas stove 62.3 μg/m^3
Ng et al. *(191)*	Adults with asthma	NO_2 levels measure while cooking: highest peak seen 500 μg/m^3; personal exposure 37.6–135.6 μg/m^3

Results
Adjusted relative rates of symptoms per 18.8 μg/m^3 increase NO_2 Classroom: Nocturnal wheeze 0.99 (0.93–1.06) Nocturnal cough 1.01 (0.98–1.04) Nocturnal asthma attacks 1.00 (0.93–1.08) Nocturnal difficulty breathing 1.11 (1.05–1.18) Kitchen: Nocturnal wheeze 1.00 (0.90–1.11) Nocturnal cough 0.99 (0.96–1.02) Nocturnal asthma attacks 1.04 (1.00–1.07) Nocturnal difficulty breathing 1.03 (1.01–1.05) Mean FEV_1 predicted –0.39% per 18-μg/m^3 increase in NO_2 No consistent evidence of interaction of NO_2 with Der p 1
Adjusted OR of any symptom per 37.6 μg/m^3 increase Single-family home: wheeze 0.99 (0.71–1.38); cough 1.07 (0.84–1.35); chest tightness 1.10 (0.78–1.57) Multi-family housing: wheeze 1.52 (1.04–2.21); cough 1.06 (0.75–1.49); chest tightness 1.61 (1.04–2.49)
Increase in FeNO: 1.6 ppb per 32-μg/m^3 increase in personal NO_2
Change in FEV_1 as percentage of predicted FEV_1: –2.45 (–1.33 to –3.57)
Highest quartile compared to lowest three quartiles: More than 4 days of symptoms in last fortnight 1.75 (1.10–2.78) in non-atopics; 1.12 (0.86–1.45) in atopics
Adjusted incidence ratio for symptoms per 37.6 μg/m^3 increase: limited speech due to wheeze 1.17 (1.08–1.27); coughing without a cold 1.15 (1.07–1.23); nocturnal symptoms 1.12 (1.04–1.19)
Fall in peak flow was related to level of NO_2 measured while cooking