

EDITORIAL

NO₂: the gas that won't go away

Nitrogen dioxide, an oxidant gas formed at high temperatures in any combustion process, has puzzled environmental health researchers for decades. At high concentrations (typically > 500–1000 µg/m³), a number of well-established effects have been observed in experimental studies. These include reduced resistance against respiratory infections [1], lung function changes in asthmatics [2], and enhanced bronchial responsiveness to allergens [3]. At the low concentrations typically encountered in the general indoor and outdoor environment, the effects are less clear.

In this issue of *Clinical and Experimental Allergy*, Ponsonby et al. [4] report that children exposed to NO₂ from gas heaters and cookers indoors were associated with a slight increase in bronchial responsiveness. The effect was more clear among children not sensitized to common allergens (notably from dust mites) than among sensitized children. This is one of the few field studies that have been able to look at measures such as bronchial responsiveness and sensitization, and it is useful to put the results in the perspective of what we have learned from other studies. I will first focus on the residential indoor environment, which is most pertinent to the findings described by Ponsonby et al. and I will then broaden the discussion to include results from recent studies on outdoor NO₂.

Research into the health effects on NO₂ indoors was prompted by early reports of associations between gas cooking and respiratory health in children living in the UK and the USA [5–8]. When it was shown that high NO₂ concentrations could be found in homes with unvented gas combustion appliances [9], NO₂, because of its well known lung toxicity, became the prime suspect in a series of studies conducted in the 1980s to further elucidate its effects [10–14]. The results of these studies have been consistent with a small effect of indoor NO₂ on lower respiratory symptoms [15], without much evidence, at the time, of effects on outcomes such as lung function in school-age children. Little evidence was found for the effects on adverse respiratory conditions in toddlers at the time [12]. Few studies were conducted among adults, generally showing even less consistency than the studies among children [10].

Interest in indoor NO₂ increased again in the 1990s when it was shown that at concentrations which fell in the upper range of levels found in gas cooker homes, NO₂ is capable of enhancing responsiveness to allergens [3,16]. A new epidemiological study suggested that among women living in homes with gas cookers, there was an increased prevalence of asthma [17]. A later, more comprehensive analysis suggested, however, that such a relationship could be found only in some centres of the large, multicentre European Respiratory Health Survey, but not in others [18].

Although NO₂ is seen as a major combustion product in the use of unvented gas-fired appliances indoors, it is not the only pollutant generated by cooking activities. Indoors, high concentrations of nitrous acid (HONO) have also been observed, without being strongly correlated to indoor NO₂ [19,20], and there is at least some evidence that HONO, at concentrations relevant to the indoor situation, can have acute respiratory effects of its own [21]. More recently, it has also become clear that gas combustion, as well as frying at high temperatures, may generate high concentrations of particles, in terms of numbers as well as mass [22]. The effects of fine and ultrafine particles in the air have received a large amount of scrutiny lately [23], and heterogeneity of findings of indoor NO₂ studies could be related to the fact that copollutants such as HONO and particles have never been measured in the indoor epidemiological studies.

In outdoor air, NO₂ is a pollutant closely related to gasoline and diesel exhaust. It has served as an indicator of traffic-related pollution in many studies, quite a few of which have suggested that at ambient concentrations, air pollution mixtures represented by NO₂ are associated with such diverse short-term outcomes as daily mortality, hospital admissions for respiratory and cardiovascular disease, cardiovascular 'events' as measured by implantable cardio defibrillators, etc. [24,25]. Studies focusing on health effects of living close to busy roads have suggested that respiratory and allergic symptoms are more frequent in children living close to busy roads, and/or near roads with high densities of 'heavy' traffic with primarily diesel emissions [26–28]. An interesting, semi-experimental study showed that allergic asthma patients, after having been exposed to traffic exhaust in a road tunnel in Stockholm for just 30 min at rest, exhibited increased bronchial responsiveness to an allergen challenge subsequent to the road tunnel exposure [29]. It should be stressed

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that in ambient air, NO₂ represents a mixture of traffic-related pollutants, and is perhaps not by itself the prime suspect of having caused the effects seen in population studies. We should seriously consider, however, whether the indoor situation is really that much different: to me it seems that the main difference is that we ignored copollutants indoors to a much greater extent than outdoors.

Where does the new study by Ponsonby et al. [4] fit in? One observation is that the indoor and personal NO₂ concentrations were quite low in this study. In view of the well-established difficulty of documenting effects on the respiratory system in experimental settings at much higher concentrations, one should express reservations as to whether this new study has really documented effects of NO₂ *per se*. As no data were presented on copollutants, one can only speculate that perhaps, other pollutants were involved. However, another study from Australia [30] failed to show effects of NO₂ in the presence of combustion by-products on airway hyper-responsiveness to histamine, at concentrations of 600–1200 µg/m³, which were almost certainly higher than the peak concentrations which may have been experienced by the subjects in the new study. The fact that the main determinant of indoor and personal NO₂ in this study seems to have been gas heaters rather than gas cookers, raises the question whether some specific contaminants could have been generated by these appliances that we have no knowledge of. Certainly, most other studies on indoor NO₂ have dealt with situations in which generally, gas cooking appliances, or gas water heating appliances have been the major source. Another feature of the Australian study is its limited sample size. Compared to previous studies in which indoor NO₂ has been measured, the sample size was small, and most effect estimates from the study do not reach conventional levels of statistical significance. We should therefore hesitate to generalize too easily: the experience of the two Jarvis papers on NO₂ and respiratory outcomes in adults [17,18] shows that a large, multicentre study may have difficulty replicating findings from a smaller, 'hypothesis-generating' study.

Another intriguing feature of the study is that effects on bronchial hyper-responsiveness (BHR) seemed to be more clear in *non*-sensitized children than in children sensitized to dust mites. This is in contrast to the experimental findings discussed earlier, and I hesitate to accept the conflicting findings of the new observational study without replication in other, preferably larger populations. So, whereas the new study provides some intriguing new pieces of information, we should remain rigorous in our scrutiny of the generalizability of what was reported. It seems that the way forward, in addition to obtaining more data on measures such as sensitization and bronchial responsiveness, also must lie in obtaining more data on the major copollutants present in indoor and outdoor mixtures –

including not only combustion-related pollutants, but also the allergens with which the combustion products may interact.

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