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## Nitrogen dioxide

# Hypothesis: Ill health associated with low concentrations of nitrogen dioxide—an effect of ultrafine particles?

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## The epidemiological associations between illness and nitrogen dioxide may be the consequence of confounding by particle numbers

In 1996 the Expert Panel on Air Quality Standards (EPAQS) recommended an ambient air standard for nitrogen dioxide (NO<sub>2</sub>) in the UK of 150 ppb measured hourly.<sup>1</sup> This recommendation, like those for carbon monoxide (CO) and sulphur dioxide (SO<sub>2</sub>) that had preceded it, was based on human toxicology rather than on epidemiology. The EPAQS was unable to find evidence that these gases were likely to be toxic to humans at the recommended concentrations. However, at the time of the NO<sub>2</sub> recommendation there was already epidemiological evidence that effects on *populations* rather than *individuals* might be associated with much lower concentrations and the EPAQS recommended that steps be taken to reduce annual average concentrations, although without proposing a long term standard. The UK government has subsequently adopted, as targets to be achieved by 2005, World Health Organization NO<sub>2</sub> guideline standards of 105 ppb (200 µg/m<sup>3</sup>) over 1 hour and 21 ppb (40 µg/m<sup>3</sup>) as an annual average, the latter having been based on possible relationships between exposure to the gas and respiratory illness in children.<sup>2</sup> Achievement of a long term standard does, of course, have the desirable consequence of reducing peaks and therefore short term exceedences.

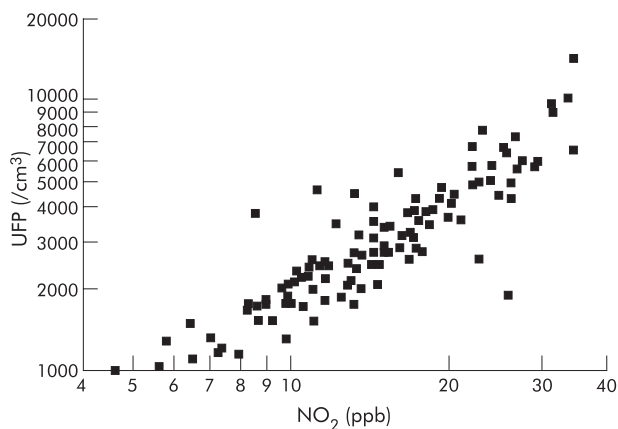
However, compliance with a very low average concentration of NO<sub>2</sub> implies a substantial reduction in the concentration of the primary pollutant released from vehicle exhausts—that is, nitric oxide (NO). Since NO reacts with ozone to form NO<sub>2</sub>, lower concentrations will result in raised urban ozone concentrations, a gas that also has known toxic effects on the lungs and that, until now, has been seen primarily as a rural pollutant in the UK.

Progressive reductions in pollution are welcomed by many because of a belief that human health and the ecology of the planet will benefit, but it must be remembered that they are attained at a cost to industry and thus to society. That cost may be offset by reductions in health expenditure, by increases in life expectancy and crop productivity, and by opportunities for the innovative in designing more efficient engines and fuels. The components of this equation can at present only be estimated very uncertainly, therefore setting tight standards tends to be an act of faith, typically driven by political balancing of the exhortations of pressure groups on both sides. This makes it particularly important to attempt to quantify the health effects of pollutants, a process that has traditionally been based on

known toxicological effects but now increasingly relies on epidemiological relationships.

## TOXIC EFFECTS OF NITROGEN DIOXIDE: EPIDEMIOLOGY OR TOXICOLOGY?

Scientific confusion arises from the different viewpoints of toxicologists and epidemiologists which may be illustrated by considering NO<sub>2</sub>. Human inhalation challenge studies have shown that normal healthy individuals do not show adverse effects to NO<sub>2</sub> below concentrations of about 2000 ppb (about 4000 µg/m<sup>3</sup>). Asthmatic subjects may react to concentrations as low as 250 ppb (about 500 µg/m<sup>3</sup>), either by alterations in bronchial reactivity or by increased sensitivity to inhaled allergens. Such subclinical changes might reasonably be expected to be associated with occasional exacerbations of asthma in very susceptible individuals in an exposed population. However, it is difficult to imagine that concentrations less than half of this could be responsible for clinically measurable episodes of illness, or that concentrations around a fifth of this could cause chronic health problems. While epidemiological studies have sometimes been able to detect associations that suggest health benefits may accrue by adhering to standards set at such very low concentrations, the overall message from these studies is confusing. For example, the WHO review in 2000<sup>3</sup> concluded that “the most consistent general impression is of increased respiratory illness in older children”. The report goes on to speculate that such episodes may set the scene for chronic lung disease in later life. This conclusion was weighted by consideration of studies of children living in houses with and without gas cookers. However, such studies have shown equivocal results, one meta-analysis having shown a significant effect<sup>4</sup> and another not.<sup>5,6</sup> As we have shown, gas cooking may entail very high acute exposures to both NO<sub>2</sub> and particles.<sup>7</sup> In fact, the heterogeneity of epidemiological findings with respect to NO<sub>2</sub> led the UK Department of



**Figure 2** Relationship between mean outdoor air 24 hour counts of particles <100 nm in diameter (UFP) and nitrogen dioxide ( $\text{NO}_2$ ) concentrations in parts per billion. Data represent 6 months of continuous side by side measurement.

We are left to argue, from toxicological considerations, which of these is likely—at the known concentrations to which individuals are exposed—to cause the observed effects. At the moment there is evidence for toxic effects of ultrafine particles at quite low concentrations in animals.<sup>17</sup> Relatively few studies have related particle numbers to cardiorespiratory illness, the most detailed being those of Wichmann's group in Erfurt, Germany. They have shown a somewhat weaker correlation between gases and particle numbers than us, but they have shown associations between numbers,  $\text{NO}_2$ ,  $\text{SO}_2$ , CO and cardiorespiratory deaths.<sup>18 19</sup> It should be noted that, in contrast to most UK cities, domestic heating in Erfurt makes an important contribution to particulate pollution in the winter and  $\text{SO}_2$  concentrations are higher. Wichmann and colleagues concluded that the apparent effects of the gases were likely to be a result of confounding.

### PARTICLES AS MICROBES – AN HYPOTHESIS

A plausible explanation for this toxicity is as follows. We hypothesise that the lung reacts to particle numbers rather than mass, since its primary defensive

role is to counter invasion by microorganisms which may be inhaled in large numbers but never in high mass. The first requirement of the lung is to kill organisms in situ and/or to transfer them to lymph nodes where immune responses may be concentrated, and ingestion by macrophages is central to this mechanism. Ultrafine particles, however, may evade this and pass directly through the alveolar wall, thus being able directly to influence endothelial cell structures. Both macrophages and endothelium release mediators that have local and more general influences, one of which is to signal that bloodstream invasion may be imminent; a systemic reaction—the acute phase response—is a consequence. If we assume that the lung treats small particles as microorganisms, it is reasonable to propose that its response relates to numbers rather than mass. By altering blood coagulability and possibly by destabilising atheromatous plaques, this systemic response may be responsible for the acute cardiac effects seen in vulnerable individuals. It seems far more plausible that these effects are a response to the number of particles rather than to  $\text{NO}_2$ , for which no comparable hypothetical explanation of effects at such low concentrations has yet been proposed.

The toxicity of microorganisms does not, of course, depend entirely on the numbers inhaled; their inherent ability to initiate cell damaging reactions or to resist defences is critically important. Similarly, not all inhaled particles would be expected to be equally toxic—for example, quartz and titanium dioxide. Thus, something other than particle numbers needs to be invoked to explain their effects, and this is likely to be the nature of the surfaces they present to the lung's defences.<sup>12 17</sup> A further step in explaining toxicity therefore requires consideration of surface properties. However, in urban air the very smallest particles make an overwhelming contribution to the total surface area, so measurement of one represents the other.

We propose that the observed associations between ill health and  $\text{NO}_2$  at low concentrations in the ambient air are the result of confounding by particle numbers. We have earlier hypothesised that a systemic response to particle inhalation is responsible for the acute cardiorespiratory effects,<sup>10</sup> a suggestion for which there is now considerable support.<sup>20</sup> This hypothesis also explains the association between air pollution and long term risk of heart disease,<sup>21</sup> since it proposes that particles cause inflammation and thus an increase in the blood of markers such as C reactive protein and fibrinogen that have been associated with increased cardiac risk. Here we propose that this is a consequence of the lung's evolutionary system of defence against microorganisms. From a practical point of view, we now need to explore relations between particle numbers and illness in order to obtain evidence upon which a number standard might be considered. For the moment, however, it seems likely that in situations such as those in most UK cities where motor vehicles are the main source of pollution, measurement of  $\text{NO}_2$  is the simplest means of assessing exposures to particle numbers and, conveniently for epidemiologists, this can be done on a personal basis.

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**Table 1** Pearson correlation coefficients for the logged daily outdoor concentrations of  $\text{NO}_2$ , NO, particle numbers,  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  in Aberdeen

	Particle numbers	$\text{PM}_{2.5}$	$\text{PM}_{10}$
No of particles <200 nm diameter		0.56 (n = 124)	0.40 (n = 121)
Nitric oxide (NO)	0.86 (n = 115)	0.45 (n = 121)	0.39 (n = 117)
Nitrogen dioxide ( $\text{NO}_2$ )	0.89 (n = 115)	0.55 (n = 121)	0.45 (n = 117)

Each box gives correlation coefficient and number of daily observations. All correlations were significant at  $p < 0.001$ .

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## Annual report

## Annual report October 2002 to September 2003

J A Wedzicha, S L Johnston, D M Mitchell

In January 2003 the Editorship of *Thorax* changed and it is with great privilege and considerable awe and trepidation that we took over as Editors.<sup>1</sup> Under the editorship of John Britton and Alan Knox *Thorax* has achieved high standards and increased its impact factor, which now stands at 4.078 (fig 1). *Thorax* is currently the most successful European respiratory journal and the third among all respiratory journals (behind the two American Thoracic Society publications). The readership of *Thorax*, together with the whole respiratory community, owes an enormous debt of gratitude to John and Alan and the previous editorial team for their outstanding achievement.

With the advent of the new editorial team, *Thorax* changed to an on-line submission system using Bench>Press.<sup>5</sup> Although there were some initial difficulties with the change over from a paper based system to complete online submission, this is now running very well and authors, reviewers, and all our editors seem to have adapted very well to the change. The number of submissions to *Thorax*

has increased, particularly from March 2003, with a total of 1260 submissions for the 12 months from October 2002 to 30 September 2003, representing an overall increase of around 33% on the previous year (tables 1 and 2). The number of original research articles submitted to the journal has increased by a similar amount. We have also seen an increase in submissions from outside the UK, especially from North America and Canada (from 74 in 2001–2 to 126 for the past year) and a doubling in the number of submissions from Asia (table 3). The median time to the first decision on a paper is 38 days. However,

the increased number of submissions means that our acceptance rate for original research papers now stands at only 12.4%.

This year we have published some important original papers and useful management guidelines for common conditions including the new BTS/SIGN (British Thoracic Society/Scottish Intercollegiate Guidelines Network) guidelines for the management of asthma in February 2003,<sup>6–7</sup> BTS guidelines for the management of pulmonary embolism,<sup>8–9</sup> BTS guidelines for the management of pleural disease,<sup>10</sup> and BTS guidelines on respiratory aspects of fitness for diving.<sup>11</sup> We have also published the *Year in Review 2002*,<sup>12</sup> and have completed the review series on the pulmonary physician in critical care,<sup>13–17</sup> continued the series on important aspects of COPD,<sup>18–28</sup> and started a series on lung cancer.<sup>29–37</sup>

A number of new features have started in *Thorax*, primarily aimed at increasing the educational value of the journal. Every month we now produce our Airwaves section at the front of the journal with short paragraphs highlighting the key messages of some of

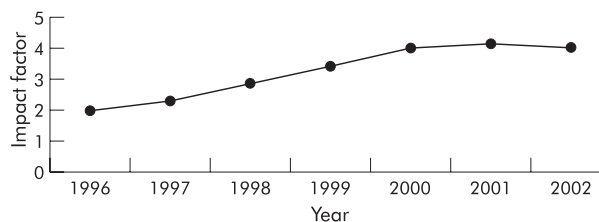


Figure 1 *Thorax* impact factor 1996–2002.