Health Effects of Gaseous Air Pollutants

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1 Introduction

Gaseous air pollutants constitute an important overall component of both outdoor and indoor air and are recognized to cause health effects, essentially in individuals with pre-existing disease. For the purposes of this chapter the gases, the primary pollutants sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and carbon monoxide (CO) with the secondary pollutant ozone, will be considered whereas acidic species will not as they are generally regarded as part of the particulate fraction. As it is likely to be the acidic nature of those species that are important in health terms, even those acids which are present in the air as a vapour phase will not be considered here.

The sources of these pollutants are important when considering health effects because sources relate to individual and population exposures. The main source of SO_2 is from fossil fuel burning, the major contributors in the UK being coal-fired power stations. Nitrogen dioxide is derived from vehicle emissions, industrial sources (including power stations) and, in the indoor environment, from combustion of gas. Although for smokers of cigarettes the major contribution to their CO exposure by far comes from their habit, in ambient air the main source is again traffic derived. Ozone is formed by the action of ultraviolet light on oxides of nitrogen and hydrocarbons, so is essentially a pollutant of the summer months in climates such as the UK but may be more perennial in countries where sunlight is present all year round. Ozone levels are generally higher downwind from a city because of the atmospheric chemistry of the formation of ozone combined with the fact that ozone, a very reactive gas, is quickly neutralized by nitric oxide in urban areas.

The health effects of gaseous pollutants have been determined in a number of different ways:

1. By chamber (human challenge) studies
2. By studies of morbidity (*e.g.* symptoms, inhaler use), usually in panels of subjects perceived to be at risk
3. From studies of hospital admissions (*i.e.* routinely collected data)
4. From studies of mortality

Chamber studies enable the effects of individual pollutants to be studied alone or in combination with other pollutants on volunteers under strictly controlled conditions. The chief advantage of this type of study is that accurate doses can be delivered and the effects of selected co-factors assessed. However, the volunteers involved in such studies are usually normal subjects or patients with mild asthma who tend to be younger, in contrast to the older subjects who are more likely to be affected by air pollution. Additionally, in chamber studies, the duration of exposure is relatively short compared to outdoor, real-life exposures and consequently it may be difficult to extrapolate findings from these types of studies to the effects that would be seen in the overall population exposed to the outdoor environment. Children are not studied in these types of experiments for ethical reasons, which prevents study of an age group where asthma is very common and in whom the health effects of pollution are often perceived to be significant. However, despite these caveats, chamber studies have, in general, provided very useful information as to the presence or absence of effects of specific pollutants at specific doses and have provided useful insights into the mechanisms of these effects.

Epidemiological studies have been much more informative about health effects both at an individual and population level, studying as they do the real-life situation. The difficulty comes in deciding how large an effect may be and to what specific pollutant or pollutant mix such an effect may be attributable. On a day-to-day basis, exposure to air pollutants may have an immediate effect, either on the same day as a rise in air pollution or perhaps delayed, lagging two, three or more days after a rise. In some situations the cumulative or average exposure over a period of three days or more may be important in determining health outcome. It is even possible that longer lags may be more important for differing health endpoints, an area which is currently being explored.

There is no doubt that there is a range of sensitivities to pollutants across different 'at risk' groups in terms of health effects of air pollution. Patients with pre-existing lung and heart disease appear to be particularly at risk, notably patients with asthma and chronic obstructive pulmonary disease (COPD). More recently, the effects of particulate pollution on patients with coronary heart disease and cerebrovascular disease have been identified, but the role of gaseous pollutants in these two disease categories is not so clear. Asthma is a common condition, affecting around 6% of the total population of the UK. In this condition, the lining of the bronchial tree is inflamed and unduly sensitive to external triggers, such as allergens in those sensitized, viral infections or physical stimuli such as exercise or inhaling cold air. Consequently, these patients are not only important as a risk group for the effects of air pollution but also act as a group where changes in lung function are frequent and measurable when trying to define the presence and size of an effect from an external stimulus. COPD is essentially a disease of cigarette smokers and although, like asthma, it is also an inflammatory condition, on a day-to-day basis these patients show no marked changes in lung function. Patients with either COPD or asthma develop symptoms because of the airway narrowing resulting from the inflammatory process. Where the baseline airway diameter is small, only minor reductions in diameter can produce marked reductions in airflow and hence symptoms.

However, it is at least intuitively logical that, for respiratory diseases, inhalation of polluted air can lead to a deterioration in symptoms.

Coronary heart disease and cerebrovascular disease share a common pathogenesis characterized by the formation of atheroma in the arteries supplying the heart or brain, respectively. In contrast to diseases of the respiratory tract, it is not entirely clear at present how inhalation of air pollutants can lead to vascular health effects, but associations have been shown between ischaemic heart disease deaths and ozone, although the major impacts in this disease area appear to derive from particulate exposure, so further discussion falls outside the remit of this chapter.

It is important to recognize that there may well be interactions between different elements of the pollutant mix in determining health effects. The statistical analysis of time series data (*i.e.* following individuals over long periods of time or considering hospital admissions and mortality over periods of time) will regard each pollutant as a separate entity acting on its own behalf. Because the possible degree of interaction of different pollutants is not known it is impossible to analyse separately for any combined effects. The studies therefore allow for the effects of all other pollutant and non-pollutant factors on that health outcome before determining a residual effect which is then attributed to that pollutant.

2 Quantification of Effect

Quantification of these effects is not easy, but certain guidelines can be used when trying to determine how much of an impact air pollution may have on the public health. A basic concept is that of a threshold. For all the gases considered here (with the probable exception of CO) the assumption has been made that at a population level the effect of the pollutant on health is linearly related and that the relationship passes through zero. Consequently, once the effect size coefficient is known for that pollutant, an estimate of overall effect on the population under consideration can be determined. These quantification estimates will vary from country to country (and almost certainly from area to area within a country) and so we will not consider this further in numerical terms here.

3 Chronic Effects

These discussions apply to the effects of short-term changes in health outcomes which can, in theory, be relatively easily recognized. In contrast, the question of whether long-term exposure over years to particular pollutants or pollutant mixes can lead to long-term health effects as yet remains to be convincingly answered, but may be more important in public health terms. The evidence for such a chronic effect with respect to gaseous air pollutants is scant, whereas there are some data with respect to long-term exposure to particulate pollution which are discussed elsewhere in this volume. Determination of chronic effects is largely dependent upon acquiring data prospectively over a matter of years (longitudinal or cohort studies). Cross-sectional studies where prevalence rates are compared between different areas at the same point in time can contribute to this question

to some extent, although they are regarded as being less powerful studies and more likely to be open to uncorrectable confounding. There are no satisfactory longitudinal studies which have considered the effects of gaseous pollutants like the Six Cities Study[1] and the American Cancer Association Study[2] have considered the effects of particulate pollution in this regard. One series of studies of Seventh Day Adventists[3] (an attractive study group as these individuals do not smoke cigarettes, thus removing the major complicating cause of respiratory and heart disease) has suggested that long-term exposure to ozone is associated, in men only, with an increased risk of developing asthma. However, this is an unusual group in an unusual setting and it is not easy to extrapolate these findings to other populations. Consequently, we will only consider the short-term effects in this chapter.

4 Sulfur Dioxide

Controlled Challenge Studies

Normal Subjects. There is consistent evidence that normal subjects are much less sensitive to the effects of inhaled SO_2 than are patients with asthma. Although one study[4] showed small increases in airways resistance at exposure of 1000 ppb (2860 $\mu g\,m^{-3}$) after a short (ten minute) exposure, other studies have failed to confirm this.[5,6] At exposures of 4 ppm or greater (11 440 $\mu g\,m^{-3}$), clear effects on airway size have been noted both at rest and with intermittent light exercise.[5,7,8] However, within these averaged group findings a wide range of individual responses can be found, suggesting that there may be individual sub-sets of normal subjects who show a greater response on exposure to this pollutant gas. The clinical significance of these effects is far from clear at present.

There are a number of different factors which may help to explain these variations in response, chief amongst which is the amount of gas entering the lower airways. It is always assumed that SO_2 is a very soluble gas and that if nasal breathing is predominant then doses to the lower respiratory tract will be much reduced because of the nasal trapping of the gas at normal ambient concentrations. A second factor is that some subjects appear to breathe more deeply on exposure to SO_2, thus increasing the dose to the lower respiratory tract. Temperature and humidity can also have a bearing in this regard, in particular cold air which can cause a degree of airway narrowing, although this is only a very small effect in normal individuals, being much more marked in subjects with asthma. However, in challenge studies the effects of these factors should be able to be kept constant between individuals and between exposures within given individuals. It is not

[1] D. W. Dockery, F. E. Speizer, D. O. Stram *et al.*, *Am. Rev. Respir. Dis.*, 1989, **139**, 587.
[2] C. A. Pope, M. J. Thun, M. M. Namboodiri *et al.*, *Am. J. Respir. Crit. Care Med.*, 1995, **151**, 669.
[3] G. L. Euler, D. E. Abbey, J. E. Hodgkin *et al.*, *Arch. Environ. Health*, 1988, **43**, 279.
[4] P. J. Lawther, A. J. Macfarlane, R. E. Waller *et al.*, *Environ. Res.*, 1975, **10**, 355.
[5] N. R. Frank, M. O. Amdur and J. Worcester, *J. Appl. Physiol.*, 1962, **17**, 252.
[6] J. F. Bedi and S. M. Horvath, *JAPCA*, 1989, **39**, 1448.
[7] J. A. Nadel, H. Salem, B. Tamplin *et al.*, *J. Appl. Physiol.*, 1965, **20**, 164.
[8] G. von Nieding, H. M. Wagner, H. Krekeler *et al.*, *Int. Arch. Occup. Environ. Health*, 1979, **43**, 195.

known whether cigarette smoking enhances or inhibits any effects of sulfur dioxide on normal subjects.[9]

Asthmatic Subjects. In patients with asthma, effects on lung function are seen at much lower concentrations. The study by Sheppard *et al.*,[10] while not demonstrating much of an overall effect, showed increases in airways resistance in two very sensitive subjects at an exposure of 100 ppb (286 $\mu g\,m^{-3}$). Other workers, exposing asthmatic subjects to 200 ppb (572 $\mu g\,m^{-3}$), showed small symptom changes but, in a further study, no changes in lung function at 200 ppb exposures associated with heavy exercise.[11] The same group of subjects were exposed to 400 ppb (572 $\mu g\,m^{-3}$) SO_2 while undergoing heavy exercise and produced small changes in lung function, but it is not until exposures to levels of around 500 ppb (1430 $\mu g\,m^{-3}$) are employed that there is clear evidence of sulfur dioxide enhancement of exercise-induced airway narrowing.[10,12,13] These responses were seen after exposures of a matter of minutes, whereas, in other studies, longer exposures (up to hours) appeared to be needed to produce an effect. These differences in effect size may be due to differing volunteer characteristics, habituation to the individual's usual air pollutant exposure resulting in tolerance to these levels of laboratory exposure (a recognized phenomenon in studies of ozone challenge) or to methodological differences.

The size of the effect in the challenge studies can be determined by measurement of lung function, the usual measures being those obtained from spirometry, namely the FEV_1 (the forced expired volume in 1 second) and the FVC (forced vital capacity). For SO_2 the results of exposure on lung function are reasonably consistent across studies, with falls of the order of 50 mL in FEV_1 from an approximate start volume of 3 litres for an exposure dose of 200 ppb of SO_2. These changes are easily reversible and the size of the effect is small, although if repeated over time these changes may become clinically significant, particularly if the pattern of induced inflammatory change was seen to be relevant to the type of inflammatory change associated with chronic asthma.

Another method of assessing the airway response to a pollutant gas is to measure the change in bronchial responsiveness (bronchial hyper-reactivity) of the individual. This can involve measuring the effect of gas exposure on the response to a non-specific irritant such as methacholine or histamine, a standard method used to characterize the severity of subjects with asthma. Alternatively, the subjects can be exposed to a range of doses of the specific gas and a curve of lung function responses constructed. The study by Horstman *et al.*[14] represents an example of the latter, taking as its main outcome measure the PC_{100} sRaw, the provocative concentration of SO_2 causing a 100% increase in specific airways resistance, a sensitive index of flow through larger intrapulmonary airways. Their results show, in a group of asthmatic subjects, a range of responses to sulfur

[9] Advisory Group on the Medical Aspects of Air Pollution Episodes (2nd report), HMSO, London, 1992.
[10] D. Sheppard, A. Saisho, J. A. Nadel *et al.*, *Am. Rev. Respir. Dis.*, 1981, **123**, 486.
[11] W. S. Linn, D. A. Shamoo, C. E. Spier *et al.*, *Environ. Res.*, 1983, **30**, 340.
[12] R. A. Bethel, D. J. Erle, J. Epstein *et al.*, *Am. Rev. Respir. Dis.*, 1983, **128**, 592.
[13] J. R. Balmes, J. M. Fine and D. Sheppard, *Am. Rev. Respir. Dis.*, 1987, **136**, 1117.
[14] D. Horstman, L. J. Roger, H. Kehrl *et al.*, *Toxicol. Ind. Health*, 1986, **2**, 289.

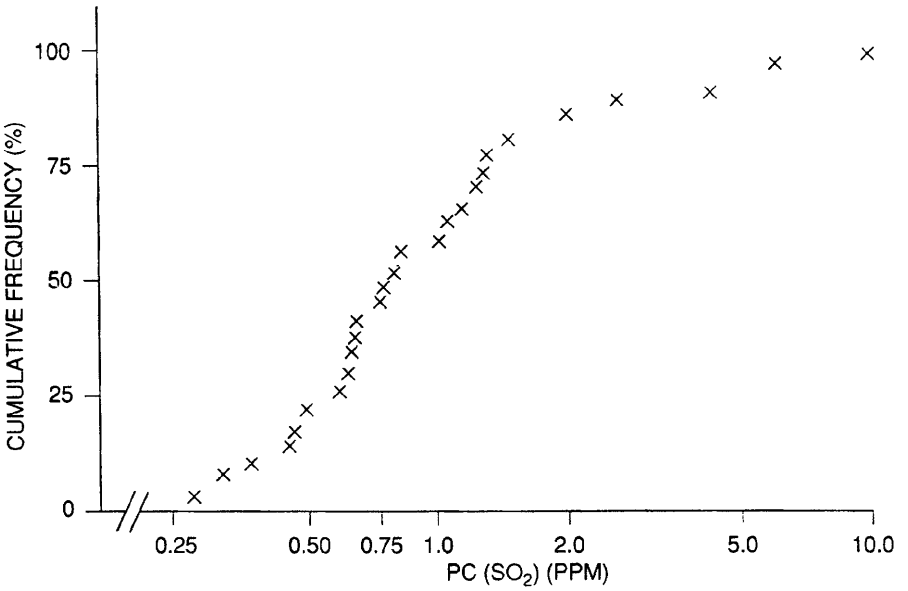

Figure 1 Distribution of individual airway sensitivity to SO_2 as cumulative percentage of 27 subjects. PC(SO_2) is the provocative concentration of SO_2 required to increase airway resistance by 20%

dioxide (Figure 1) with a median PC_{100} sRaw of 750 ppb (2145 $\mu g\,m^{-3}$). However, the usual concentrations of sulfur dioxide seen in ambient air in the UK rarely exceed 120 ppb (343 $\mu g\,m^{-3}$) nowadays, although occasionally, during episodes, levels in excess of 200 ppb have been recorded.

Extrapolating the findings from the chamber studies to the effects on public health is, therefore, somewhat difficult, particularly as those most susceptible to the effects of air pollution (*i.e.* those with more severe disease) are not used in challenge studies. It is likely that these more severely affected individuals have a much lower threshold for developing symptoms or changes in lung function on exposure to air pollution. Consequently, controlled chamber studies can be used to show whether effects in response to a pollutant challenge could occur in a given group of subjects, but extrapolation to all potential members of such a group in real life would be unwise.

Mechanisms. The way in which sulfur dioxide can result in these pathological changes in the airway are likely to be multiple and in some individuals a particular mechanism may be more important than in others. Animal studies[9] show that SO_2 can activate mucosal sensory nerves, leading to airflow obstruction both by central neural reflex and by local axon reflex changes (neurogenic inflammation). Although it is likely that these effects are also true for man, there is no direct work to confirm this. SO_2 may also act by non-neural mechanisms with mucosal damage leading to release of inflammatory mediators, perhaps attracting inflammatory cells, notably neutrophils and eosinophils, to the airway wall.

Morbidity Studies

Studies on morbidity (*i.e.* changes in symptoms and treatment use) are conducted by establishing a cohort (panel) of susceptible individuals and following them prospectively over a period of weeks or months. Over this time the individual will record symptoms twice daily and, in most studies, a measure of lung function such as peak expiratory flow. This approach produces a large amount of data over time at both an individual and a group level. A second way of assessing the response to ambient changes in air pollution is to study individuals during an air pollution episode. However, the quality of information in the latter situation is generally less good as the study is by definition retrospective and opportunistic.

The most important study in the field of panel studies from a methodological point of view was that undertaken by Whittemore and Korn,[15] who clearly spelt out the considerable problems in attributing health effects which were small in size when having to allow for other exposures which could have similar size or greater effects (*e.g.* passive cigarette smoke exposure, exposure to animals in sensitized asthmatic subjects). They also stressed the importance of allowing for other pollutants when trying to assess the effects of a given pollutant using multiple regression analysis to try and pick out a signal from the noise. Many studies, however (and this applies to epidemiological studies such as those assessing hospital admissions and mortality), use single pollutant models in their analysis rather than two or multi-pollutant models. However, providing the potential shortcomings of the methodological approaches are recognized, these studies do inform on the problems of determining these generally small health effects. This method of analysis has been followed by many subsequent researchers who have also, with variable success, attempted to deal with confounders and co-exposures in panel studies. Most of these studies have, however, been undertaken in children, either specific groups of subjects with asthma or school summer camp studies where a variable number have asthma. A significant problem comes when recruiting subjects for such studies and having to define whether a child with respiratory symptoms should be regarded as having asthma or another diagnosis, such as episodic bronchitis. In some studies, this problem has been circumvented by classifying subjects into those with and without symptoms.[16] Studies in adults are infrequent.

The size of any effect needs to be quantified in relation to the air pollutant exposure and estimates have been expressed as a change per unit change in pollutant, for a larger change in level (*e.g.* per 10 $\mu g\,m^{-3}$ rise in particles) or for a change over the interquartile range over which the levels of that pollutant were measured during the running of that particular study. Unfortunately, these different approaches mean that it is not always possible to undertake comparisons between studies. Because most of the studies from the US and Canada have been undertaken in the summer, the main pollutants assessed have been particles, ozone and aerosol strong acid (the ozone studies being discussed below), SO_2 being regarded until lately by North American workers as an unimportant pollutant for their countries, largely on the basis of low measured ambient levels.

[15] A. S. Whittemore and E. L. Korn, *Am. J. Public Health*, 1980, **70**, 687.
[16] S. Vedal, M. B. Schenker, A. Munoz *et al.*, *Am. J. Public Health*, 1987, **77**, 694.

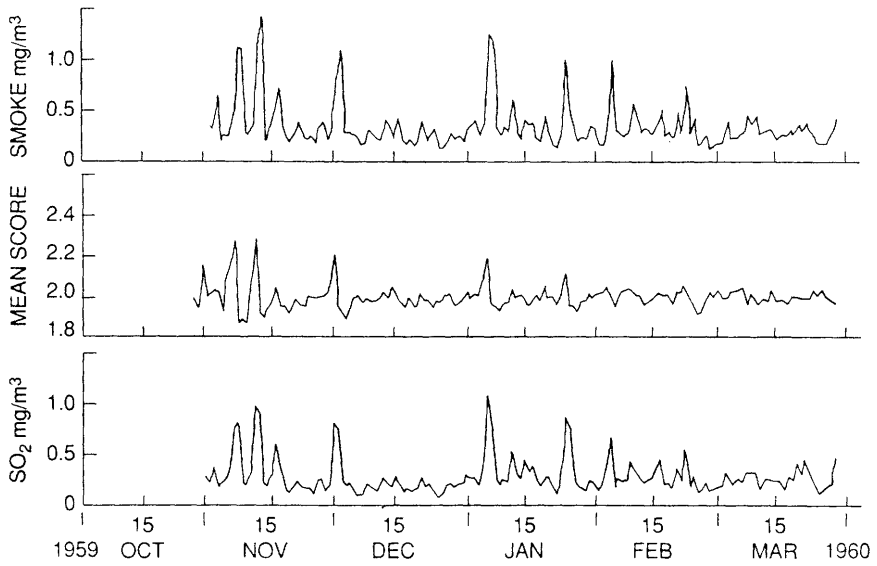

Figure 2 Daily change in symptom score in patients with chronic bronchitis over time in relation to levels of SO_2 and black smoke

Where SO_2 has been considered by US workers, health effects were usually absent (summarized in ref. 17). In one study of symptomatic and asymptomatic children in Pennsylvania,[18] reductions in peak flow of the order of 0.9 L min^{-1} were identified for an increase in SO_2 of 15 $\mu g\,m^{-3}$ (5 ppb). The baseline value of peak flow in this group was of the order of 300 L min^{-1} and such a fall is clinically insignificant on a day-to-day or one-off basis. European panel studies have shown effects relating to SO_2 in three of four studies,[19–22] but with effect sizes of similar degree. The Manchester study[22] also suggested that those with more severe asthma (as measured by bronchial responsiveness) were more likely to show an effect of SO_2, although particulate levels were not measured in this study and the SO_2 effect could be due to particles alone.

In the early 1960s, when SO_2 levels were around 300 $\mu g\,m^{-3}$ (105 ppb) with regular peaks to 1000 $\mu g\,m^{-3}$ (350 ppb), a series of panel studies of patients with chronic bronchitis (now defined as chronic obstructive pulmonary disease, or COPD) showed quite marked day-to-day correlations between symptoms and levels of both smoke and sulfur dioxide (Figure 2).[23] The symptom scoring system was fairly simple but proved robust. When a similar group of patients were studied some 10 years later when sulfur dioxide levels had dropped to around 200 $\mu g\,m^{-3}$ (70 ppb) [with only rare excursions above 500 $\mu g\,m^{-3}$ (175 ppb)], the day-to-day changes in symptoms were not perceptibly correlated. This suggested

[17] Committee on the Medical Effects of Air Pollutants, *Asthma and Outdoor Air Pollution*, HMSO, London, 1995.
[18] L. M. Neas, D. W. Dockery, J. D. Spengler *et al.*, *Am. Rev. Respir. Dis.*, 1992, **145**, A429.
[19] W. Roemer, G. Hoek and B. Bruenkreef, *Am. Rev. Respir. Dis.*, 1993, **147**, 118.
[20] A. Peters, U. Beyer, C. Spix *et al.*, *Am. J. Resp. Crit. Care Med.*, 1994, **149**, A662.
[21] S. M. Walters, J. G. Ayres, G. Archer *et al.*, *Am. J. Respir. Crit. Care Med.*, 1994, **149**, A661.
[22] B. G. Higgins, H. C. Francis, C. J. Warburton *et al.*, *Thorax*, 1993, **48**, 417.
[23] R. E. Waller, *J. R. Coll. Physicians London*, 1971, **5**, 362.

that either effects were no longer present at these background levels or, more likely, that they were not detectable using this fairly crude methodology. However, the apparent absence of measurable changes suggests that on a day-to-day basis such levels of SO_2 will not cause problems in the majority of subjects with COPD, although the question of the effects of exposures at this level over longer time periods remains.

Air pollution events featuring sulfur dioxide are now rare in the western world, although where there is considerable burning of fossil fuels these events may be more frequent. The London fog incident of 1952[24] was associated with huge exposures to SO_2 (3 ppm) and resulted in very substantial increases in mortality and morbidity, although discussion still takes place as to whether the particles, sulfur dioxide or the acidity of the pollutant mix was the most responsible component. A study from Holland of an event occurring in the late 1960s[25] showed a clear and significant reduction in lung function in normal subjects during and following an air pollution episode when SO_2 levels rose to 300 $\mu g\,m^{-3}$ (105 ppb). The degree of loss was 150 mL in FEV_1, an approximate 5% loss. More importantly, this loss of lung function was still present two weeks later, although it returned to normal thereafter. Later studies from the same country[26,27] showed similar effects also in normal subjects. More recent air pollution events in the UK have been associated with relatively modest increases in sulfur dioxide. The London event of 1991[28] showed increases in sulfur dioxide to around 125 ppb, although the Birmingham event of 1992 was associated with levels of around 250 ppb.[29] The London event was associated with a 10% increase in all cause mortality, but the only measurable health effect at the primary care level was a small increase in consultations for sore throat. Particles appeared to be the most important causal factor, sulfur dioxide not having an effect once particles were accounted for. The Birmingham study[29] considered two panels of subjects with mild and with severe asthma and was followed using daily diary cards over the period of the pollution episode. There were no discernible effects on the patients with mild asthma but those with severe asthma showed a significant fall in lung function during the period despite increasing their inhaled and oral therapy. It would appear that pollution events where SO_2 was increased, at an individual level, may have limited effects except in those with more severe disease, although there still appears to be some discrepancy between studies from different countries. This again flags up the difficulty in extrapolating the findings from air pollution studies from country to country, at least in quantitative terms.

In 1990 the WHO determined that for sulfur dioxide levels of around 200 $\mu g\,m^{-3}$ (70 ppb), small transient reductions in lung function could be seen in children and adults that could last for as much as two to four weeks, but the magnitude of the effect was small at around 2–4%. However, because airborne levels of sulfur dioxide and particulate matter move so clearly together over time

[24] Ministry of Health, HMSO, London, 1954.
[25] R. van der Lende, C. Huygen, E. J. Jansen-Koster *et al.*, *Bull. Physiopathol. Respir.*, 1975, **11**, 31.
[26] B. Brunekreef, M. Lumers, G. Hoek *et al.*, *JAPCA*, 1989, **36**, 1223.
[27] G. Hoek, B. Brunekreef, P. Hofschreuder *et al.*, *Toxicol. Ind. Health*, 1990, **6**, 189.
[28] H. R. Anderson, E. S. Limb, J. M. Bland *et al.*, *Thorax*, 1995, **50**, 1188.
[29] S. M. Walters, J. Miles, J. G. Ayres *et al.*, *Thorax*, 1994, **48**, 1063.

and space, the WHO found it difficult to apportion these effects entirely to the gas or the particle phase. Their interpretation of the research available up to that time led them to state that if levels of SO_2 reached 250 $\mu g\,m^{-3}$ (87 ppb) there was a measurable increase in respiratory morbidity amongst susceptible adults with COPD and perhaps also in children, these figures being more marked when levels reached around 400 $\mu g\,m^{-3}$ (140 ppb).[30]

Hospital Admissions

The re-emergence of SO_2 as an important air pollutant has largely occurred as a result of the series of multicentre studies called the APHEA studies (Air Pollution and Health, a European Approach). The cities involved ranged from Helsinki in the north to Barcelona in the south. Although there were some methodological differences across the cities involved in the study in terms of data acquisition, the statistical approach was uniform and as robust as could be for the data. In the event, the consistency and coherence of the results suggest that the findings are not only valid but also very important, at least as regards determination of effects in the European setting. The data are expressed as a relative risk for a standard increase in pollutant and was taken as 50 $\mu g\,m^{-3}$ for all pollutants including SO_2.[31] For all respiratory admissions the overall effect for all cities involved for this increment in SO_2 was 1.009 (95% confidence interval 0.992–1.025) for individuals between the ages of 15 and 64 increasing to 1.020 (1.005–1.046) for those over the age of 65.[32] To put this into a clinical context, these admissions relate essentially to patients with COPD or asthma, the former making by far the largest contribution. For COPD, such patients have pre-existing disease, whereas in asthma the patients affected may be a mix of those with moderate to severe disease through to those with milder asthma who, on the day of the increase, may not have had adequate self-treatment available. A similar effect was seen during the outbreak of asthma attacks seen in the UK in 1994 during a thunderstorm.[33] An increase in admissions of 2% on a day when SO_2 increases by 50 $\mu g\,m^{-3}$ represents a very small risk at an individual level but can result in a significant effect in public health terms, assuming that the relationship between admission and pollutant level is linear through zero, which is generally accepted to be the case for SO_2. However, there was considerable heterogeneity of results for SO_2 in this study across the cities involved, the more homogeneous results being seen for ozone (see below). These findings are in contrast to the study from Birmingham,[34] which showed more of an effect from black smoke than SO_2, although a small effect of the gaseous component of the pollutant mix was seen in that study. Further breakdown of the APHEA studies for asthma and for COPD perhaps add a little clarity to the picture. For COPD, the relative risk for six cities was 1.022 for SO_2 (for a 50 $\mu g\,m^{-3}$ rise) although the confidence intervals around this estimate embraced unity. However, for Paris, Milan and Barcelona the risk was

[30] World Health Organization, European Series No. 43, Copenhagen, 1992.
[31] C. Spix, H. R. Anderson, J. Schwartz *et al.*, *Arch. Environ. Health*, 1998, **53**, 54.
[32] R. Newson, D. Strachan, E. Archibald *et al.*, *Thorax*, 1997, **52**, 680.
[33] S. Walters, R. K. Griffiths and J. G. Ayres, *Thorax*, 1994, **49**, 133.
[34] H. R. Anderson, C. Spix, S. Medina *et al.*, *Eur. Respir. J.*, 1997, **10**, 1064.

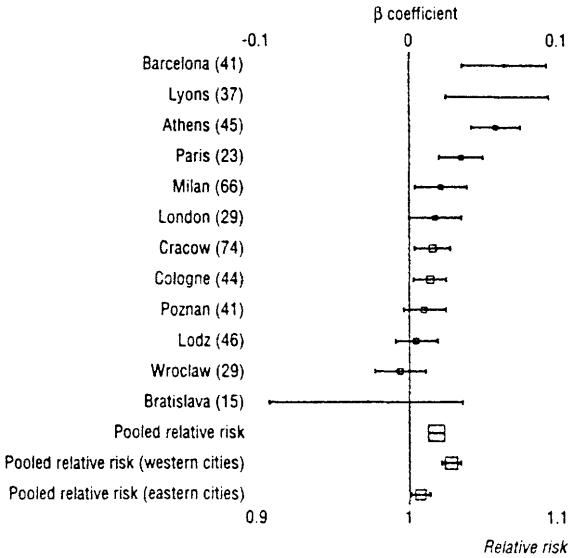

Figure 3 Estimated individual city and pooled relative risks of mortality associated with an increase in SO_2 level of $50\,\mu g\,m^{-3}$. Numbers in brackets are median values for SO_2 and the size of the point representing each relative risk is inversely proportional to its variance

higher and statistically significant.[35] For asthma the effect size was smaller still and did not achieve statistical significance.[36] This may be a feature of the smaller numbers of asthma admissions compared to those for COPD.

Mortality

Data from the severe smogs of the 1950s in the UK and from other parts of the world enabled the WHO[37] to consider that increases in daily deaths become discernible when 24 hour average concentrations of sulfur dioxide exceed about 175 ppb SO_2 ($500\,\mu g\,m^{-3}$) with equivalent levels of black smoke. It was always deemed a matter of concern that extrapolating from these historical data to the 1990s was unwise, but recent studies by the APHEA group have shown that sulfur dioxide consistently emerges as a factor for mortality.[38] In western European cities, a 3% (95% CIs 2–4%) increase in daily mortality (all causes) was found for a $50\,\mu g\,m^{-3}$ rise in either SO_2 or black smoke. However, in eastern European cities the effects were much smaller (Figure 3) with an increase in all cause mortality of just 0.8% (95% CIs -0.1 to $+2.4$%) for the same rise in SO_2. These effects were seen whether assessing a same-day effect or a cumulative effect over 2–4 days.

It is important to realize that exposure to air with higher levels of air pollutants will contribute to death by bringing forward the time of death. Patients with COPD, for instance, who die on days of higher pollution will already have severe pre-existing disease. Consequently it is likely that the time of death may have been brought forward by only a small amount, perhaps days. On the other hand,

[35] J. Sunyer, C. Spix, P. Quenel *et al.*, *Thorax*, 1997, **52**, 760.
[36] World Health Organization, Environmental Health Criteria No. 8, Geneva, 1979.
[37] K. Katsouyanni, G. Touloumi, C. Spix *et al.*, *Br. Med. J.*, 1997, **314**, 1658.
[38] Advisory Group on Medical Aspects of Air Pollution Episodes (3rd report), HMSO, London, 1993.

patients with coronary heart disease may have unsuspected pre-existing severe disease and perhaps at a young age and it is possible that, in this group of patients, death may be brought forward by as much as years. This applies when considering the effect of any pollutant on mortality.

Summary

In challenge studies, SO_2 has a clear effect on airway function, particularly in patients with asthma. While it was believed for many years that this gas was no longer an important pollutant with respect to health effects because of the marked reductions in ambient levels produced by Clean Air Act legislation throughout the world, recent evidence, particularly from Europe, has shown that SO_2 impacts on people with pre-existing disease, particularly respiratory disease. Despite ambient levels of SO_2 which are very low compared to those seen in Western European countries in the 1950s and 1960s, these effects can be identified and range from changes in symptoms to hospital admissions and mortality. From the health point of view, attention needs to be paid to the control of a pollutant which is not vehicle generated.

5 Nitrogen Dioxide

Controlled Challenge Studies

Exposure of normal subjects or subjects with pre-existing lung conditions to nitrogen dioxide in the challenge situation has generally resulted in no changes in either lung function or symptoms at low to moderate levels of exposure, although very high levels (in excess of 2 ppm) can result in some changes in certain, presumably susceptible, individuals.

Normal Subjects. In normal subjects a wide range of studies with exposures of 1000 ppb or less over periods ranging from 20 minutes to two hours had no effect on any lung function measurement or index of bronchial responsiveness.[39] At a range of exposures between 1.5 ppm for three hours up to 7.5 ppm for two hours, non-specific bronchial responsiveness to methacholine was increased to a small extent.[40–42] These effects do not appear to be affected by increasing age, but no studies have been undertaken in children to address the lower end of the age spectrum.

Patients with COPD. In this group of patients the findings are more variable. In some studies, exposure to high levels (1.5 ppm) of NO_2 (2820 $\mu g\,m^{-3}$) showed an increase, albeit small, in airways resistance,[43] while a dose–response study with

[39] M. Beil and W. T. Ulmer, *Int. Arch. Occup. Environ. Health*, 1976, **38**, 31.
[40] V. Mohsenin, *Arch. Environ. Health*, 1988, **43**, 242.
[41] M. W. Frampton, P. E. Morrow, C. Cox *et al.*, *Am. Rev. Respir. Dis.*, 1991, **143**, 522.
[42] W. S. Linn, J. C. Solomon, S. C. Tree *et al.*, *Arch Environ. Health*, 1985, **40**, 234.
[43] G. von Nieding, M. Wagner, H. Krekeler *et al.*, *Int. Arch. Arbeitsmed.*, 1971, **27**, 338.

doses ranging from 0.5 to 2 ppm over an hour with 30 minutes exercise showed no effect; similar findings have been found in a number of other studies.[38]

Asthmatic Subjects. The findings in asthmatic subjects are not too dissimilar from those found in normal subjects. Apart from one study[45] of exposure to 100 ppb of NO_2 for one hour, which appeared to increase methacholine responsiveness, the majority of studies up to and including exposure to 4 ppm have shown no change in lung function and no change in bronchial responsiveness.[38] However, there are a few studies[46–50] where some change in bronchial responsiveness did occur with exposures between around 250 and 500 ppb for durations ranging between 30 minutes and three hours. More recently, nitrogen dioxide exposure at a level of 400 ppb has been shown to enhance the subsequent response to allergen challenge,[51] suggesting that NO_2 on its own probably has very limited effect, even in patients with asthma, when acting directly, but may act as a priming agent to other co-exposures such as allergen challenge, with sensitized subjects showing an enhanced (+ 5%) bronchoconstrictor response to allergen challenge following NO_2 compared to air.

Mechanisms. The mechanism of any priming effect is not entirely clear at present. There is some evidence that eosinophils are recruited and activated on exposure to NO_2[52] and some suggestion of alteration in inflammatory cell sub-sets in bronchial alveolar lavage fluid following NO_2 exposure. Further work is needed to explore this subtle potential effect of exposure to this pollutant gas.

Morbidity

The findings for morbidity are inconsistent and this has led to some lack of conviction that any effect shown of NO_2 on symptoms or treatment use is in fact due to residual confounding rather than a genuine effect. It is felt by many that the most likely explanation of this dissimilarity in results is that day-to-day changes in morbidity indicators associated with NO_2 are in fact causally related to another pollutant which moves closely with nitrogen dioxide in terms of ambient levels. Perhaps the most likely is another index of ultrafine particles such as $PM_{1.0}$ or particle numbers.[53] However, many studies have found associations between NO_x linked pollution and health effects and at levels well below the WHO guidelines.

It is probably inappropriate, therefore, to regard NO_2 as a gas which we can be confident about identifying as a cause of day-to-day changes in morbidity on

[44] W. S. Linn, D. A. Shamoo, E. L. Avol *et al.*, *Arch. Environ. Health*, 1985, **40**, 313.
[45] J. Orehek, J. P. Massari, P. Gayrard *et al.*, *J. Clin. Invest.*, 1976, **57**, 301.
[46] G. Bylin, T. Lindvall, T. Rehn *et al.*, *Eur. J. Respir. Dis.*, 1985, **66**, 205.
[47] M. A. Bauer, M. J. Utell, P. E. Morrow *et al.*, *Am. Rev. Respir. Dis.*, 1986, **134**, 1203.
[48] V. Mohsenin, *Toxicol. Environ. Health*, 1987, **22**, 371.
[49] G. Bylin, G. Hedenstierna, T. Lindvall *et al.*, *Eur. Respir. Dis.*, 1988, **1**, 606.
[50] R. Jorres and H. Magnussen, *Eur. Respir. J.*, 1990, **3**, 132.
[51] W. S. Tunnicliffe, P. S. Burge and J. G. Ayres, *Lancet*, 1994, **344**, 1733.
[52] J. L. Devalia, R. J. Sapsford, D. R. Cundell *et al.*, *Eur. Respir. J.*, 1993, **6**, 1308.
[53] J. G. Ayres, *Eur. Respir. Rev.*, 1998, **8**, in press.

present evidence. However, the longer-term effects of nitrogen dioxide exposure, particularly when one bears in mind that oxides of nitrogen are major products of gas combustion in kitchens and levels are also elevated in rooms with a poorly serviced gas fire, may be more important in determining chronic health effects.

There have been many studies going back a number of years[54,55] showing that respiratory symptoms in population studies were more noticeable in homes with gas fired kitchens. More recently, one of the UK centres of the European Respiratory Health Study[56] showed that in women (although not in men) respiratory symptoms were greater in those who had gas fired kitchens compared to those with electrically powered homes. There was a tendency for the symptoms to be worse in those who were atopic (*i.e.* sensitized to allergens), although this did not quite achieve statistical significance. More extensive analysis of the full European project has, however, shown that this finding is not uniform across all the geographical areas studied.

Cross-sectional studies of disease prevalence can provide information on the effects in populations differentially exposed to air pollutants. A good example is the series of studies of re-unified Germany, where the population of old Eastern Germany was previously exposed to high levels of SO_2 and black smoke compared to the higher exposures in Western Germany to NO_x.[57] The association between a higher prevalence of productive cough (bronchitis) in children with SO_2 in Eastern Germany and of NO_2 in Western Germany with asthma and hayfever initially led to the, probably incorrect, assumption that NO_2 was a cause of asthma and other allergic diseases. Studies over time, when SO_2 and black smoke levels have declined considerably in old Eastern Germany, have shown a fall in the prevalence of bronchitis in children but no increase in asthma or hayfever. Apart from being fairly certain that the older, sulfurous, air pollution did lead to mucus hypersecretion, these figures do not yet help us in determining whether NO_2 has a role to play in the aetiology of allergic diseases.

Hospital Admissions

The findings from a range of studies of hospital admissions or attendances to Accident & Emergency Departments are similar to those from the morbidity studies. The majority show no effect at all, while others do find associations for a range of conditions with day-to-day changes in NO_2 levels.[38] A study from Vancouver[58] did find a correlation between A&E attendances for respiratory disease in subjects over the age of 60, but NO_2 levels were strongly correlated with other pollutants. A European study[59] showed that for a $10\,\mu g\,m^{-3}$ rise in NO_2, hospital attendances for croup increased by around 4%, but the association was as strong for particles and it is difficult, given these findings, to separate out either as the more important causal pollutant.

[54] R. J. W. Melia, C. du V. Florey, D. G. Altman *et al.*, *Br. Med. J.*, 1972, **2**, 149.
[55] R. J. W. Melia, C. du V. Florey, R. W. Morris *et al.*, *Int. J. Epidemiol.*, 1982, **11**, 164.
[56] D. J. Jarvis, S. Chinn, C. Luczynska *et al.*, *Lancet*, 1996, **347**, 426.
[57] E. von Mutius, Ch. Fritzsch, S. K. Weiland *et al.*, *Br. Med. J.*, 1992, **305**, 1395.
[58] D. V. Bates, M. Baker-Anderson and R. Sizto, *Environ. Res.*, 1990, **51**, 51.
[59] K. Katsouyanni, A. Karakatsani, I. Messari *et al.*, *J. Epidemiol. Community Health*, 1990, **44**, 321.

Mortality

Where NO_2 has been associated with changes in mortality, associations have also been shown with other pollutants so that disentanglement of the true effects pollutant by pollutant is not possible.[38] The APHEA studies[37] have not been helpful in this regard as insufficient NO_2 data were available measured over suitable time sampling frames. However, the current set of epidemiological studies (APHEA 2) will hopefully be able to consider the role of NO_2 in this respect, although the likelihood is that any effect possibly due to NO_2 will be inseparable from the effects due to other pollutants.

Summary

In summary, while it is attractive to view NO_2, an oxidant pollutant, as a cause of health effects, the evidence from challenge and epidemiological studies do not show significant health effects. It is likely, however, that longer-term exposures, especially in the indoor setting, may have an impact in terms of chronic effects, maybe by a permissive mode of action allowing other stimuli to have a greater effect on the individual.

6 Carbon Monoxide

Mechanisms

Unlike the other gaseous pollutants covered in this chapter, the mechanism whereby CO exerts an effect on human health is well understood, at least at the level of its ability to bind to haemoglobin. More recently, to a certain extent as a result of studies of CO in the outdoor environment and its health effects, suggestions have been made that this gas may also act in a different way, although a satisfactory alternative mechanism has yet to be supplied.

In toxic doses, such as might be encountered in severe poisoning, the first sign is loss of consciousness. If death does not then ensue, some patients are left with cerebral damage of variable degree, with a wide range of symptoms and clinical signs. These effects are due to the formation of carboxyhaemoglobin (COHb) in red blood cells, at levels which can be measured in blood or, indirectly, measured as CO in exhaled breath. In normal, unexposed subjects, COHb levels are 1% or below. Cigarette smokers may have levels ranging from 4% to 15%, depending on the number of cigarettes smoked. Consequently, many smokers will contribute to ambient levels, their exhaled breath CO concentrations exceeding that of ambient air.

Challenge Studies

At COHb concentrations of 2.5–4.0%, effects have been seen on maximal exercise duration in fit healthy men;[60] at levels slightly higher, patients with angina find that episodes of chest pain occur earlier during exertion than when their COHb is

[60] J. A. M. Turner and M. W. Nicol, *Respir. Med.*, 1993, **87**, 427.

in the normal range. It has thus been believed that ambient levels of CO producing COHb levels below 2.5% are unlikely to exert any deleterious effects even in patients with coronary heart disease. This level would be achieved by breathing 10 ppm CO for 8 hours, 25 ppm for 1 hour, 50 ppm for 30 minutes or 87 ppm for 15 minutes.

Morbidity Studies

Recently, reports from North America and London suggest that hospital admissions for heart failure are related to ambient levels of CO, increasing by around 23% for a 10 ppm rise in CO.[61] Studies from Athens and Los Angeles also show an effect on all cause mortality, with effect sizes ranging from 4 to 11.5% for a 10 ppm rise in CO.[61] These findings are difficult to interpret, given the current knowledge of mechanisms. Either the result is spurious, being due to residual confounding, or the effect is real and due to the fact that those patients with severe congestive cardiac failure are very sensitive to small changes in COHb, or there is an alternative mechanism whereby CO is acting on these patients. Given that many patients with cardiac failure are smokers of cigarettes, and the dose delivered to the lung in these subjects from their habit hugely exceeds ambient exposures, these findings might imply that unrecognized confounders may explain these results rather than it being a specific effect in susceptible groups, but targeted studies stratified by disease severity would help to address this issue.

Summary

Ambient CO exposure is generally low in urban areas compared to exposure to CO through actively or passively inhaled cigarette smoke, and although some epidemiological evidence would suggest that, perhaps in certain susceptible individuals with heart disease, ambient levels can be associated with health effects, the mechanisms for these findings are far from clear. It would be prudent, however, to consider further these possible health effects, making careful allowance for co-exposures, to determine whether these effects are real or spurious.

7 Ozone

Controlled Challenge Studies

One of the main differences between ozone—a highly reactive, oxidant gas as far as the airways are concerned—and sulfur dioxide with respect to challenge data is that ozone appears to affect both asthmatics and normal subjects equally, whereas sulfur dioxide is much more likely to cause airway narrowing in patients with asthma.[62] Inflammatory changes have been shown histologically in the bronchial mucosa in animals at ozone concentrations as low as 80 ppb. Other animal work suggests that, at much higher exposures, irreversible pulmonary

[61] Committee on the Medical Effects of Air Pollutants, *Quantification of the Effects of Air Pollution in the UK*, The Stationery Office, London, 1998.

[62] Advisory Group on the Medical Aspects of Air Pollution Episodes (1st report), HMSO, London, 1991.

fibrosis or emphysema can occur.[63] In the human setting, however, most studies have involved normal or mild asthmatic subjects undergoing fairly strenuous exercise in an ozone chamber for several hours, trying to reproduce the sort of exposure that might occur during periods of persistently high ozone levels in the normal environment.

Normal Subjects. At doses varying between 80 ppb and 600 ppb for periods ranging from one hour to six hours, there is evidence of increases in specific airways resistance at the higher end of the range of exposures and also enhancement of non-specific responsiveness to both histamine and methacholine.[64–66] However, there is wide variation in the response to ozone within the subjects constituting the normal groups in these studies. For instance, in the study by Horstman *et al.*[65] the fall in FEV_1 after exposure to 120 ppb of ozone for over six hours ranged from zero in about one third of the subjects to 37%. Whether smokers are more susceptible than non-smokers to higher concentrations of ozone remains unclear.[67]

Asthmatic Subjects. Studies in asthma have looked at similar types of exposures both in terms of dose and duration and the co-existence of exercises, the normal studies. However, although there are changes in airways resistance,[68,69] these results are generally small and appear to be of the same order as normal subjects. One interesting finding is that repeated exposures on consecutive days appear to be related to the amelioration of effects on symptoms in patients with asthma, suggesting a role for the development of tolerance to ozone in those repeatedly exposed.

More importantly, ozone appears to act as a permissive agent by enhancing the response to another co-exposure. The best example of this is a response to allergen, particularly grass pollen, as grass pollen levels in ambient air in most temperate countries will be elevated during times when ozone events are more likely to occur. The best study characterizing this response[70] covered 24 asthmatic subjects, 12 with allergic rhinitis and 10 controls, exposing them to ozone (250 ppb) or filtered air and assessing the effect on subsequent grass pollen challenge. In the asthmatic subjects, the amount of allergen required to reduce FEV_1 by 20% was lower by a factor of 1.74 after ozone compared to air challenge, with similar changes in the rhinitis group. This is similar in extent to the changes found for NO_2 and house dust mite allergen challenge[51] and provides a coherence of evidence for this more subtle effect of gaseous air pollutants. The use of grass pollen challenge with ozone is very relevant as in many temperate climates the ozone levels are only significantly increased during the summer

[63] B. E. Barry, F. J. Miller and J. D. Crapo, *Lab. Invest.*, 1985, **53**, 692.
[64] L. J. Folinsbee and M. H. Mazucha, in *Atmospheric Ozone Research and its Policy Implications*, eds. T. Schneider, S. D. Lee, G. J. R. Wolters and L. D. Grant, Elsevier, Amsterdam, 1989.
[65] D. H. Horstman, L. J. Folinsbee, P. J. Ives *et al.*, *Am. Rev. Respir. Dis.*, 1990, **142**, 1158.
[66] M. J. Holtzman, J. H. Cunningham, J. R. Sheller *et al.*, *Am. Rev. Respir. Dis.*, 1979, **120**, 1059.
[67] M. Hazucha, F. Silverman, C. Parent *et al.*, *Arch. Environ. Health*, 1973, **27**, 183.
[68] J. W. Kreit, K. B. Gross, T. B. Moore *et al.*, *J. Appl. Physiol.*, 1989, **66**, 217.
[69] J. Q. Koenig, D. S. Covert, Q. S. Hanley *et al.*, *Am. Rev. Respir. Dis.*, 1990, **141**, 377.
[70] R. Torres, D. Nowak and H. Magnussen, *Am. J. Respir. Crit. Care Med.*, 1996, **153**, 56.

months when grass pollen counts or grass allergen levels in the air are increased. The concentration of ozone used in this study is high compared to the usual ambient ozone levels (even during high ozone spells) found in such areas of the world, but this study has at least shown that such an effect does occur. More recently, studies employing lower dose allergen challenge over longer time exposures, producing more realistic environmental co-exposures, have been undertaken which suggest that potentiation of allergen response by gaseous pollutants can still be identified (V. Strand, personal communication).

Mechanisms. Being an oxidizing gas, ozone is known to enhance inflammation in both the proximal and distal intrapulmonary airways, but the exact mechanism by which this occurs is still undetermined. There is evidence that ozone induces airway neutrophilia in normal subjects at doses of 200[71] to 300 ppb[72] for one hour and these changes are more likely to be seen in asthmatic compared to normal subjects.[71] In addition, a range of pro-inflammatory cytokines and markers of inflammation (*e.g.* Il8, GM-CSF and myeloperoxidase) are released into the airways during ozone challenge, again being more marked and more widespread in asthmatic subjects.[71] More recently, ozone exposure at 160 ppb has been shown to induce eosinophil infiltration in the airways of asthmatic subjects, the eosinophil being the crucial inflammatory cell in asthma.[73] A single exposure to ozone is thus able to induce or enhance inflammation in the airways of both normal and asthmatic subjects but more so in the latter where inflammation already exists. It is not known what occurs in repeated or chronic exposure, although repair systems will undoubtedly come into play to reduce or modify the response.

Morbidity Studies

Most of the studies of ozone on day-to-day changes in symptoms and treatment use have come from North America, largely from children attending summer camps. These often have a preponderance of asthmatic subjects but by no means always. Again, there is a range of responses both in terms of lung function and in symptoms. Lung function has shown changes over a range of 0.1–1.1 mL ppb^{-1} in forced vital capacity and approximately the same deficit for the forced expiratory volume in one second (FEV_1). For peak flow the changes vary between 3 and 7 mL s^{-1} ppb^{-1}.[62] These are very small changes and in general are unlikely to be noticed at a clinical level. These mean data, however, do cover a wide range of response. For instance, Figure 4[74] shows that the median decline in forced vital capacity was 5 mL ppb^{-1} ozone (range -20 to $+25$ mL ppb^{-1}). This suggests that there may be susceptible sub-populations who are more responsive to ozone and tends to match the findings from the challenge studies.

The data on those panel studies where adults have been the subjects are very

[71] C. Scannell, L. Chen, R. M. Aris *et al.*, *Am. J. Respir. Crit. Care Med.*, 1996, **154**, 24.
[72] E. S. Schelegle, A. D. Siefkin and R. J. McDonald, *Am. Rev. Respir. Dis.*, 1991, **143**, 1353.
[73] D. B. Peden, B. Boehlecke, D. Horstman *et al.*, *J. Allergy Clin. Immunol.*, 1997, **100**, 802.
[74] P. L. Kinney, J. H. Ware, J. D. Spengler *et al.*, *Am. Rev. Respir. Dis.*, 1989, **139**, 56.

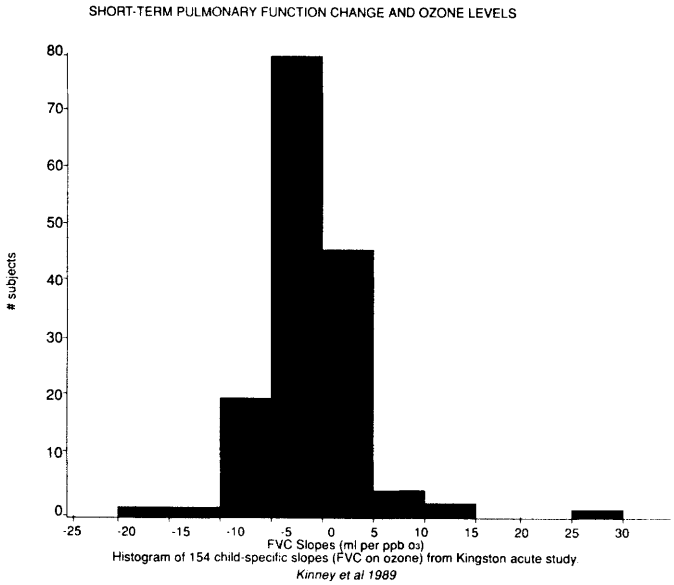

Figure 4 Distribution of changes in FVC ($mL\,ppb^{-1}$ ozone change) in children

limited. One UK study showed no effect of ozone on either symptoms or lung function.[21]

As far as symptoms are concerned, some studies have demonstrated more marked changes in symptoms than in lung function, some showing a dose–response relationship. A study from Los Angeles, where ozone exposure is high and persistent, showed that symptoms of chest discomfort and cough increased by around 25% when levels exceeded 300 ppb, but that above 400 ppb, chest discomfort increased by more than twofold and cough by 77%.[75] However, even at lower levels of exposure, relationships can be found between symptoms such as breathlessness and ozone exposure.[76]

Hospital Admissions

The first indication that ozone might have an impact on hospital admissions came from studies in Canada,[58,77] where it was more the acidic component of the summer pollutants that appeared to be correlated to hospital admissions for asthma rather than ozone itself. Further studies in the UK (London) failed to show an effect of ozone on hospital admissions for cardiovascular diseases,[78] although other studies (see ref. 79) have shown small but significant positive associations. For example, London data from different years suggested a relative risk for admission of 1.04 for a 25 ppb increase in ozone concentration. A modelling process using this coefficient has suggested that, in the UK, if using a 50 ppb threshold, ozone was involved in about 0.25% of all respiratory

[75] J. Schwartz and S. Zeger, *Am. Rev. Respir. Dis.*, 1990, **141**, 62.
[76] B. Ostro, M. Lipsett, J. Mann *et al.*, *Am. J. Respir. Crit. Care Med.*, 1994, **149**, A658.
[77] D. V. Bates and R. Sizto, *Environ. Res.*, 1987, **43**, 317.
[78] J. D. Poloniecki, R. W. Atkinson, A. Ponce de Leon *et al.*, *Occup. Environ. Med.*, 1997, **54**, 535.

admissions, although if no threshold was assumed this estimate increased by about 20-fold.[79]

Mortality

Data from London for the years 1987–1992 have shown an effect of ozone on all cause, respiratory and cardiovascular mortality, particularly during the warmer months.[80] The increases were expressed as the % change in mortality for a change from the 10th to the 90th centile of the measured levels, which yielded values of 3.5%, 3.6% and 5.4% for all cause, cardiovascular and respiratory mortality, respectively. These findings were independent of the effects of other pollutants but might appear to be difficult to square with the lack of effect seen for hospital admissions. The reasons for this difference are not as yet understood.

Summary

Ozone is an important pollutant in terms of health effects, with clear impacts at all levels of morbidity and an effect on bringing forward death. It is a seasonal pollutant and thus has a much greater effect in the summer months in temperate climes but is a year-round pollutant in areas with long hours of sunshine. It should be regarded as a non-threshold pollutant so that health effects can in theory be seen at all levels to zero.

8 Overall Conclusions

The most important gaseous pollutants with respect to human health are SO_2 and ozone, at least in terms of acute effects. Both seem to affect patients with respiratory disease, affecting asthmatic subjects at the level of symptoms, although with less of an effect on attacks severe enough to result in hospital admissions, and patients with COPD, particularly those with severe disease, resulting in hospital admission and advancement of death. The evidence for NO_2 exerting an effect on health on a day-to-day basis is weak but it may play a role, particularly when considering indoor exposures, on chronic respiratory disease states. If these health effects are to be ameliorated, attention needs to be paid as much to sources of SO_2 (power stations) as of ozone (vehicle emissions), while for NO_2 the quality of indoor air needs to be addressed.

[79] J. R. Stedman, H. R. Anderson, R. W. Atkinson *et al.*, *Thorax*, 1997, **52**, 958.
[80] H. R. Anderson, A. Ponce de Leon, J. M. Bland *et al.*, *Br. Med. J.*, 1996, **312**, 665.