Research Report TM/04/03
December 2004

A review of the acute and long term impacts of exposure to nitrogen dioxide in the United Kingdom

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This review addressed the distinction between the impact of nitrogen dioxide (NO_2) on health from that of particles and the availability of concentration-response information for long term exposure to NO_2.

The results of animal studies suggest that damage to lung lining fluid may occur at concentrations of NO_2 that are marginally higher than those in ambient air. Serious respiratory effects occur only at much higher concentrations. Peak concentrations are more important than longer term mean levels of exposure and, although damage tends to increase with duration of exposure, there is evidence of adaptation.

The results of human volunteer experiments show that concentrations of NO_2 that are slightly higher than in ambient air affect lung function, airways resposiveness, respiratory symptoms and the response of asthmatics to allergens.

The power of epidemiological studies to determine a relationship between ambient NO_2 and health has been weakened by the poor correlation between personal exposure and ambient concentrations and the importance of tobacco smoke as a source of NO_2 exposure for smokers. The small apparent short term effect of NO_2 on health appears to be independent of that of particles, but may partly due to some other unmeasured component of traffic pollution. Ambient NO_2 in the UK may be associated with an increase in daily death rate and numbers of hospital admissions for cardiovascular or respiratory illness of less than 0.2% and probably less than 0.05%. There is limited evidence to suggest that the impacts of particles on daily death rate are enhanced by NO_2.

The results of studies of the long term effects of exposure to NO_2 do not suggest an adverse effect.

CONTENTS

1. INTRODUCTION AND AIMS

1.1 INTRODUCTION

This review was undertaken to address two of the topic areas in the 2001 Department of Health call for proposals to undertake research into the health effects of air pollution:

> Are there sufficient high quality studies on the long term effects of nitrogen dioxide to allow the selection of a dose-response function for quantification?
>
> Has recent evidence made the distinction between the effects of nitrogen dioxide on health from those of particles any easier?

The review included assessment of exposures to nitrogen dioxide (NO_2) in relation to the interpretation of epidemiological investigations of the effects of NO_2 and the quantification of impacts. It also included a review of the strength of the toxicological and epidemiological evidence that appears to link short and long term exposure to NO_2 to adverse health effects. This included assessment of the potential effect of NO_2 in modifying the relationship between airborne particles and health.

It was believed that a preliminary estimate of the scale of the effects associated with exposure to NO_2 and the secondary products of NO_x emissions would be important to the overall assessment of the public health impacts of NO_x emissions and of the benefits of improved control of NO_x emissions. The report therefore includes a quantitative assessment of the influence of NO_2 on public health in the UK and a brief assessment of the indirect influence of NO_x emissions on health that arises as a result of the formation of ozone and PM_{10} (as secondary nitrate).

1.2 BACKGROUND

There is a general consensus that airborne particles are the most important pollutant in the relationship between air pollution and health. A number of studies have, however, demonstrated apparent associations between ambient concentrations of NO_2 and health. The APHEA (Air Pollution and Health, a European Approach) project, for example, found associations between NO_2 and increased daily mortality, cardiovascular mortality, hospital admission and exacerbation of asthma in children (Sunyer et al, 1997; Anderson et al, 1997; Touloumi et al, 1997). Concentrations of NO_2 in ambient air, however, are often closely correlated with those of particles such that it is difficult to demonstrate an independent effect. Results from the second stage of APHEA suggest that NO_2 may have an important influence on the association between particle concentrations and daily mortality (Katsouyanni et al, 2001). Other studies have found apparent health effects associated with nitrogen oxides (NO_x) in indoor air, but it is unclear whether effects are specifically linked with NO_x or some other pollutant arising from gas cooking. The results of experiments with human volunteers suggest that adverse effects may be possible during exposure to extremely high concentrations of ambient NO_2. Health and Safety Executive (2003) have recently issued a Chemical Hazard Alert Notice for NO_2 to address concerns about the possible development of emphysema in workers exposed to NO_2.

The Government's Air Quality Strategy has led to a number of local authorities declaring Air Quality Management Areas specifically because of NO_2. An understanding of the true importance of NO_2 in the association between air pollution and health is therefore important to ensuring that maximum benefit is derived from the continuing development of the National Air Quality Strategy.

1.3 AIMS

The aims of the study were to:

Assess the evidence for an independent role for NO_2 in the association between air pollution and health;

In, particular, assess the evidence for an association between long term exposure to NO_2 and adverse health effects;

Determine if recent evidence clarifies whether NO_2 has a significant modifying effect on the relationship between airborne particles and health;

Undertake a preliminary quantification of the scale of health impacts associated with direct exposure of the UK population to ambient NO_2; and

Comment on the potential magnitude of health impacts associated with the secondary products of NO_x emissions, specifically ozone and particulate nitrate.

1.4 REPORT STRUCTURE

The early chapters of the report discuss issues of exposure to NO_2 and related pollutants and the results of animal and human volunteer studies. The main part of the report describes the epidemiological evidence linking short and long term exposure to NO_2. The short term studies are described first because of the much greater availability of information than for long term effects. The information from the short term studies provides a useful background to the studies of long term effects. The epidemiological reviews are followed by a preliminary quantification of the potential health impacts of NO_2 in the UK. Each of these chapters is concluded by a brief discussion and a more substantial discussion is provided in the penultimate chapter. The final chapter describes the conclusions of the study.

1.5 UNITS

Concentrations of NO_2 are given in μgm^{-3} throughout the report. Where the study originally quoted ppb, the conversion factor used was 1.913, the conversion factor at 20^oC.

2. METHODS

2.1 LITERATURE REVIEW

2.1.1 General

Initially existing reviews by the World Health Organisation (WHO, 1997) and others (MAAPE 1993, 1995; Lipfert 1994; American Thoracic Society 1996) were read and the key evidence linking NO_2 to effects assessed**.** Standard literature searches using "Medline" and "Pollution and Toxicology" were undertaken to identify more recent studies relevant to understanding the potential health effects that may be associated with exposure to NO_2. The abstracts of these studies were screened to identify those of most relevance to the study aims. Studies that examined the long term effects of NO_2, the interaction between NO_2 and particles and those reporting concentration-response functions for either NO_2 or particles together with concurrent concentrations of both pollutants were identified as being of particular interest.

2.1.2 Exposure assessment

Information about exposure to NO_2 was reviewed to inform the epidemiological review and also the quantification.

Levels of exposure to ambient NO_2 in the UK were reviewed using information available from DETR's review of the air quality strategy (DETR et al, 2000), the National Air Quality Archive (www.airquality.co.uk) and studies of personal exposure to NO_2 in the UK and elsewhere in Europe that were identified using Medline. The relationship between personal exposure and ambient concentrations was specifically investigated because of its relevance to the interpretation of concentration-response information in epidemiological studies. It is also relevant to understanding the uncertainty associated with the estimation of impacts associated with ambient NO_2 in the UK.

A brief review was made of the potential contribution of NO_x emissions to secondary nitrate and ozone formation in the UK and the exposure concentrations of these substances within the UK. This included limited consideration of the secondary products of UK NO_x emissions in Europe and secondary pollutants found in UK air that originate in European air masses. These issues were fully reviewed by the Photochemical Oxidants Review Group (PORG) in 1997. Further quantification of the relationship between UK NO_x emissions and ozone formation has been undertaken in a series of more recent studies published on the air quality website (www.airquality.co.uk).

2.1.3 Animal toxicology and human volunteer experiments

Toxicological information was reviewed to understand the levels of exposure to NO_2 likely to cause adverse effects, the types of effect that might arise from exposure, potential mechanisms by which NO_x might cause adverse effects and the interaction between NO_x and particle pollution. Evidence of the potential toxic mechanisms by which NO_2 might cause adverse effects was assessed and used in the overall consideration of the medical plausibility of the apparent associations between ambient NO_2 and health and the possibility of NO_2 modifying the effect of particles. Both animal studies and human volunteer (chamber) studies were considered, starting from existing reviews by the WHO (1997), MAAPE (1993, 1995), and the American Thoracic Society (1996) and updating by using abstracts identified using Medline. The animal studies included a limited number of investigations of the effects of combined exposure to particles and NO_2.

2.1.4 Epidemiology

Copies were obtained of recent papers identified by the literature search as containing relevant concentration-response information for NO_2 and for particles. These included studies of both indoor and outdoor air quality. Consideration was given to reported levels of NO_2, particles and other pollutants, uncertainties in exposure estimation and the relationship between concentrations of NO_2 and those of particles or other pollutants. Exposure concentrations in the review studies were compared with those prevalent in the UK. Individual studies were examined to collect information from which an assessment could be made of the relationship, if any, between concentration-response functions reported for NO_2 and a range of potential influences on that relationship including mean concentrations of NO_2 and PM_{10} and any concentration response function determined for PM_{10}. In addition, individual studies were examined to investigate whether there is a typical lag between changes in ambient concentrations of NO_2 or particles and apparent effects. This could potentially be informative in terms of understanding the mechanisms by which NO_2 may cause damage and improve linkage with the findings of toxicological experiments.

The review assessed the strength of any reported associations between NO_2 and health, the evidence linking apparent effects specifically to NO_2 and the level of uncertainty associated with any reported concentration-response information. This included assessing reviewing the apparent effects of pollutants in single and multipollutant models and concentration-response relationships found for particles at different levels of NO_x and vice versa. We investigated whether the types and scale of effects associated with indoor and outdoor exposures to NO_2 were consistent and the strength of evidence linking effects to NO_2 as opposed to some other measured or unmeasured pollutant. The key outputs from the epidemiological part of the review were an evaluation of the strength of evidence for concentration-response functions linking both short term and long term exposure to ambient NO_2 to a range of health-endpoints and specific functions to use in the quantification of effects. In terms of an evaluation of the size of the potential effects of NO_2, more weight was given to the findings of reviews than to those of individual studies.

2.2 QUANTIFICATION OF HEALTH EFFECTS ASSOCIATED WITH DIRECT EXPOSURES TO NITROGEN DIOXIDE

A relatively simple approach was taken to quantification that was judged to be sufficient to indicate the scale and importance of the direct effects of exposure to NO_2. Given the large number of sources of uncertainty within the exposure estimations and concentration-response functions, the costs of a more sophisticated approach could not be justified at this time. The information from the exposure assessment, toxicology and epidemiology reviews was integrated to assess the plausibility of the concentration-response information, the evidence that relationships are causal and the relevance of the concentration-response information to current levels of environmental exposure to NO_2 in the UK. The concentration-response information was used to quantify the potential effects of NO_2 associated both with short term high pollution events and longer term exposure. Consideration was given to the use of different concentration-response functions for cities with different levels of particle pollution, but no evidence was found that particle concentrations have an important modifying effect on concentration-response relationships for NO_2.

The impact of day to day variability in concentrations of NO_2 in the UK was quantified in terms of the summed short term effects over 12 months. The approach was similar to that used by other investigators (eg IGCB, 2001) in that concentration-response functions for short term effects (normally over 24 hour periods) were applied to annual mean concentrations of NO_2. This takes account of the mean variability of NO_2 concentrations but assumes that the variability of concentrations is more important than specific high pollution events. A correlation would be expected between the number and intensity of high pollution events and

annual mean concentrations (but see section 3.3). The concentration-response functions are generally expressed in terms of an incremental change in a given health point per unit change in pollutant concentrations so that in order to calculate the actual number of cases, background rates of the relevant health endpoint were required. National rates of mortality and hospital admission were readily available, but relevant information for other health endpoints was more difficult to acquire. Some information about respiratory illness was obtained from the British Thoracic Society's website and information was obtained from a number of studies reporting concentration-response functions.

Basic demographic information for the UK by local authority area and by region was downloaded from the National Office of Statistics website. Estimates of annual mean concentrations of NO_2 and of PM_{10} were made for local authority areas and groups of local authority areas were made using tabulated concentrations for UK monitoring stations for 1998 (DEFRA et al, 2000). In addition mapped concentrations from the Local Air Quality Management pages of the air quality website (www.airquality.co.uk) were used to inform the estimates. Short term effects of NO_2 were calculated in terms of the total number of cases per year by using the selected concentration-response functions. It was assumed that levels of NO_2 (5 μgm^{-3}) and PM_{10} in remote rural areas were representative of the natural background. The calculation of annual effects for each area therefore was of the form:

> population x background prevalence of effect x (annual mean concentration of NO_2 minus 5 μgm^{-3}) x increment in effect per μgm^{-3} NO_2.

The estimated effects for a range of health endpoints were then summed for the whole of the UK. Consideration was given to the sources of uncertainty in the estimated impacts and the scale of these uncertainties in relation to calculated effects. This included consideration of the estimation of population exposure, uncertainties in the concentration-response functions and baseline health of the exposed population and uncertainties with respect to attribution of effects to NO_2 or some other component of traffic pollution.

There was insufficient concentration-response information for the long term effects of NO_2 for a quantification to be undertaken. It was possible, however, to make some comments about the probable scale of effects.

2.3 ESTIMATION OF THE INDIRECT HEALTH EFFECTS ASSOCIATED WITH NO_X EMISSIONS

The relationships between NO_x emissions and concentrations of ozone, acidity and particulate nitrate were reviewed. Given that UK emissions of NO_x have relatively little influence on UK concentrations of these secondary pollutants, it was not possible to estimate the UK population mean exposure to these pollutants that can be attributed to UK NO_x emissions. A qualitative assessment of the health importance of each of the secondary pollutants was made but it was not possible to compare the direct effects of ambient NO_2 with those arising from exposure to secondary products of NO_x pollution.

3. EXPOSURE ASSESSMENT

3.1 INTRODUCTION

This chapter discusses the factors that influence personal exposure to NO_2. Two main issues are addressed: current levels of exposure to NO_2 in the UK and the reliability of exposure estimates used in the derivation of concentration-response functions in epidemiological studies. Epidemiological studies of the effects of nitrogen dioxide have used a range of exposure metrics: personal exposure concentrations of NO_2, concentrations of NO_2 in indoor air, presence/absence of a gas cooker in the home and concentrations of NO_2 in ambient air. This has led to issues relating to the comparability of exposure-response functions derived using different measures of exposure. There are also issues with respect to confounding exposures as these would be different in indoor and outdoor environments. Smoking is also likely to be an important influence on personal exposure.

The first part of this chapter summarises information about concentrations of NO_2 in UK air, the relationships between concentrations of NO_2 and those of other pollutants and concentrations of secondary pollutants formed as a result of NOx emissions. This is of relevance to the quantification of the potential effects of NO_2 in outdoor air in the UK (chapter 8) and to understanding how potential confounding exposures might mask or enhance the effects of NO_2 in ambient air. The second part of chapter discusses personal exposures to NO_2. The main findings of the studies of personal exposure to NO_2 in ambient and in indoor air are summarised and the implications for the interpretation of epidemiological issues are discussed. This chapter was originally drafted before DEFRA's Air Quality Expert Group (AQEG) produced its 2003 report on nitrogen dioxide and more information about NO_2 in UK air can now be obtained from this report.

3.2 MEASUREMENT ISSUES

A range of methods are available for measuring concentrations of NO_2 and each technique is subject to its own limitations (see WHO 1997 and more recent review by AQEG, 2003). The EU Reference method is based on continuous monitoring using chemiluminescence. Diffusion tubes are much cheaper to deploy but do not provide the time resolution required for the investigation of the effects of high pollution events. They do, however, allow for the ready evaluation of the spatial variation of NO_2 concentrations within an urban area. Measurement of NO_2 concentrations with passive diffusion tubes may lead to under or over estimation of concentrations relative to those measured with chemiluminescent instruments. Local authorities in the UK are required to undertake comparative measurements to allow bias correction of diffusion tube data. The AQEG have reviewed the relationship between the two methodologies and found that the main source of difference is the laboratory that undertakes the preparation and analysis of tubes. Other sources of difference include whether tubes are deployed for 1, 2 or 4 weeks, whether sites are exposed or sheltered, the time of year, total concentrations of NO_2, the ratio of NO_2/NO_x and whether tubes are sited at roadside or background locations. Several types of passive NO_2 sampler are subject to interference by nitrous acid (Spicer et al, 2001). Chemiluminescent monitors are subject to interference by both peroxyacetyl nitrate (PAN) and nitrous acid (AQEG, 2003). Both chemiluminescent monitors and diffusion tubes have been used in epidemiological studies of the effects of ambient NO_2. Personal exposures have been measured in epidemiological studies using personal diffusive badges, of which several types are available.

In addition to some minor uncertainties with respect to measurement methods, compliance with monitoring protocols may have a substantial influence on estimated personal exposure concentrations. Lambert et al (1994) reported a noncompliance rate of about 40% associated

with the placement and use of samplers by parents involved in a major survey of children's respiratory health.

The main implication of the differences in measurement methods used in different epidemiological studies is that absolute exposure concentrations may not be directly comparable with respect to differences of less than 5 μgm^{-3}, but greater apparent differences in concentration are likely to be real. Chemiluminescent measurements (as normally used in time series studies) are likely to be more comparable across studies than other types of measurement, provided that adequate quality control measures were in place. Measurements made with diffusive samplers may be subject to some within study inconsistencies arising from seasonal factors and various aspects of sampler location.

3.3 NITROGEN DIOXIDE IN OUTDOOR AIR

3.3.1 Sources and sinks

The major source of NO_x in ambient air is traffic emissions (48% of total UK NO_x emissions in 1997; DETR et al, 2000). Large stationary combustion plants are important sources of NO_x with power stations contributing 20% of total NO_x emissions in the UK. Transport emissions dropped by almost 90% during the 1990s and are expected to continue to decrease during the early years of the 21st Century (DETR et al, 2000).

3.3.2 Ambient concentrations in the UK

Regional variation

Annual mean concentrations of NO_2 in the UK range from less than 5 μgm^{-3} to more than 50 μgm^{-3} (www.airquality.co.uk). There was a gradual decline in NO_2 concentrations during the 1990s (Loader, 2000). The highest concentrations of NO_2 arise in the middle of the large conurbations: London, Reading, the West Midlands, Leeds, Manchester and Liverpool. Concentrations in other major cities such as Glasgow and Newcastle are also relatively high. More generally concentrations of NO_2 are raised in the more densely populated areas of the UK and along the route of the most heavily trafficked motorways (Fig. 3.1). The average concentrations of NO_2 measured using diffusion tubes by local authorities in 2000 were 39, 27 and 22 μgm^{-3} at roadside, intermediate, urban background sites respectively. The spatial variation in NO_2 concentrations is moderately well correlated with that of the primary pollutant NO_x (Fig. 3.1). Overall, it would appear that concentrations of NO_2 are closely correlated with traffic density. This is consistent with traffic being a major source of NO_2 and also highlights the potential problem of separating the impacts of NO_2 from other components of traffic pollution. In terms of the quantification of the impacts of ambient NO_2 (see chapter 8), effects might be expected to be greatest in urban areas where both the highest concentrations of NO_2 arise and the highest population densities are present.

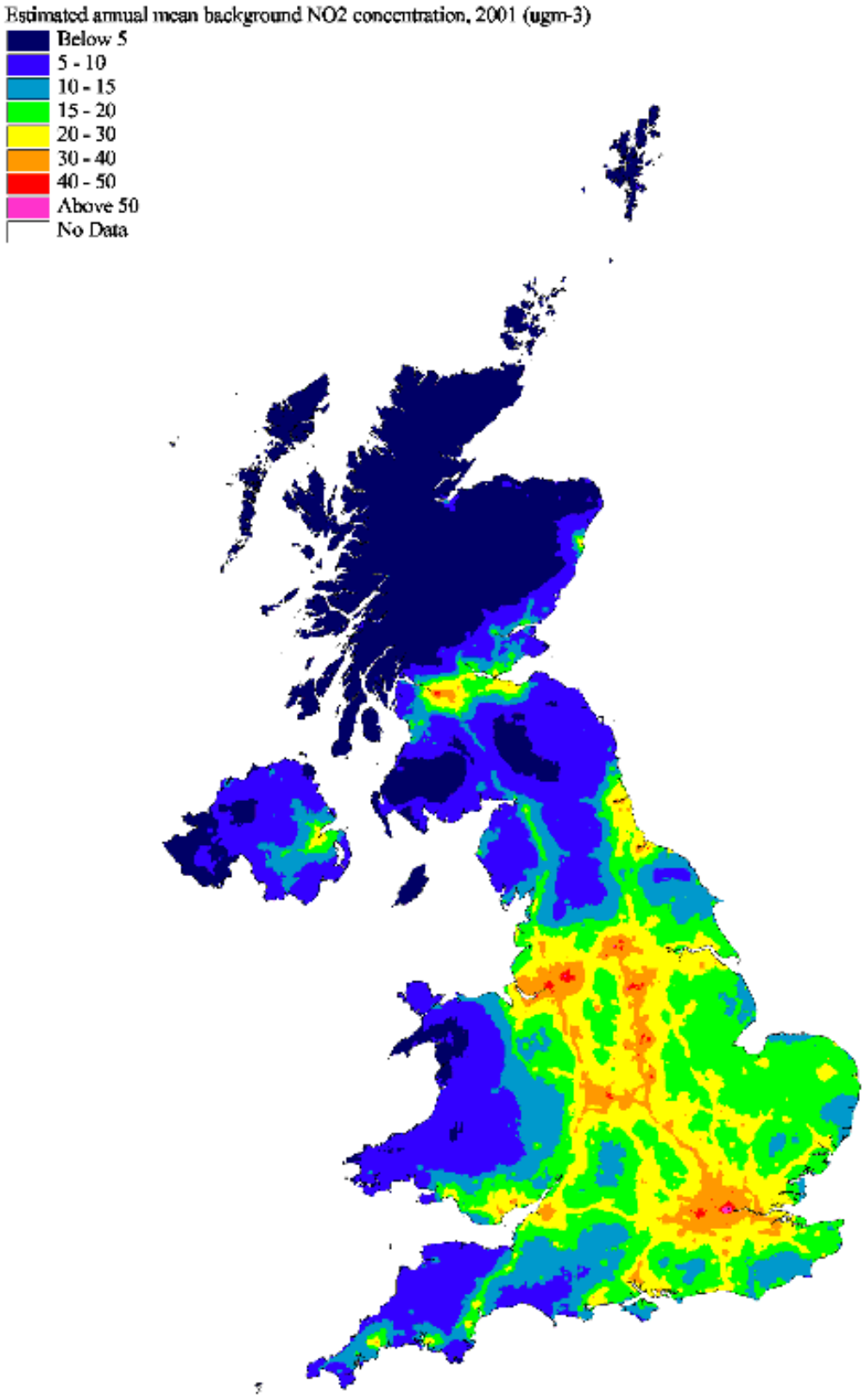

Figure 3.1: Modelled regional variation in concentrations of NO_2 within the UK (NETCEN map for 2001)

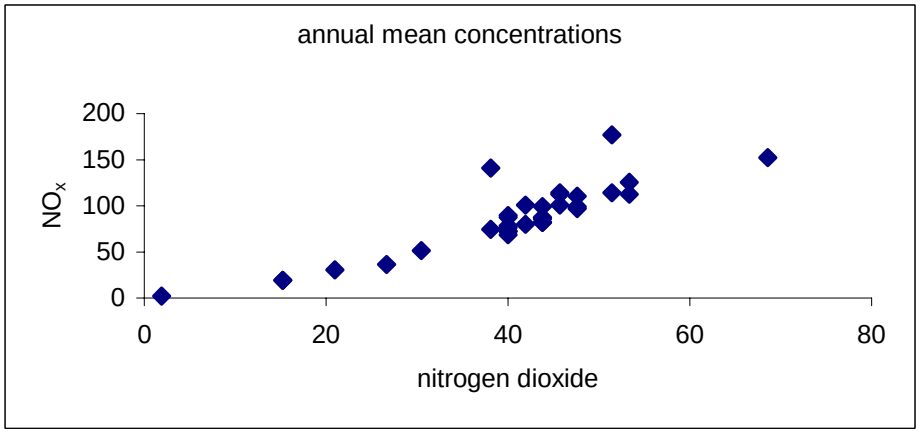

Figure 3.2: Relationship between annual mean concentrations (µgm^{-3}) of NO_x and NO_2 at UK monitoring stations (1996 data)

In general terms the spatial variation in annual mean concentrations of NO_2 is poorly correlated with that of particles measured as PM_{10} and that of NO_x is only weakly correlated with that of particles (Figure 3.3). Although traffic emissions and other combustion processes are important sources of NO_x (or NO_2) and particles, concentrations of these pollutants are also substantially affected by the formation of secondary particles and the long distance movement of pollutants. High levels of particles in an individual UK city may originate from high emissions of primary pollutants elsewhere in the EU. This suggests that in the UK, it should be possible to conduct epidemiological studies that separate the effects of NO_2 and total PM_{10}. It may not, however, be possible to separate the effects of NO_2 and primary particles arising in vehicle exhaust (not measured).

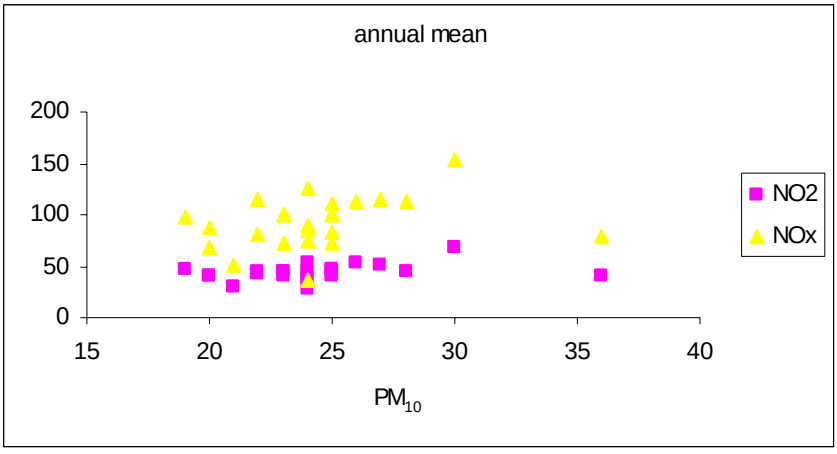

Figure 3.3: Relationship between annual mean concentrations (µgm^{-3}) of particles and NO_x / NO_2 (1996 data)

There is a clear inverse relationship between the spatial distribution of annual mean concentrations of ozone and those of nitrogen dioxide (Fig. 3.4) and a weaker relationship between peak concentrations (98th percentile) of these pollutants. This is consistent with the increased depletion of ozone at higher NO_x concentrations. It also implies that populations, that are exposed to relatively high mean levels of NO_2, are not generally also exposed to relatively high mean concentrations of ozone and vice versa.

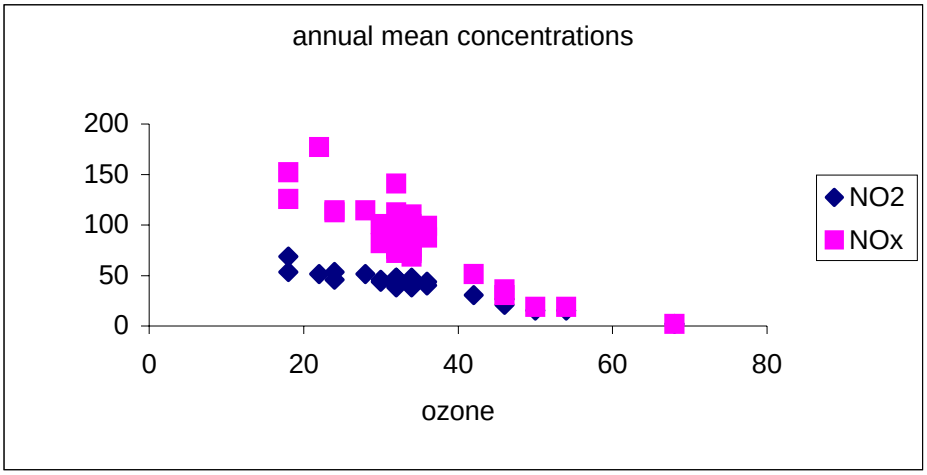

Figure 3.4: Relationship between annual mean concentrations (µgm^{-3}) of ozone and nitrogen dioxide (1996)

Diurnal variation

The diurnal variation in NO_2 concentrations affects the potential peak concentrations that might be experienced for periods of an hour or less during high pollution events. These peak exposures have not been well investigated in epidemiological studies and cannot be easily included in any quantification of effects. They are, however, of direct relevance to understanding the relationship between the exposure concentrations used in short term experiments and potential exposures in ambient air. The diurnal variation of NO_2 concentrations is also of relevance to understanding the sources and sinks for NO_2 in ambient air, the formation of secondary pollutants from ambient NO_x and relationship between short term exposure concentrations of NO_2 versus those of other pollutants.

Concentrations of NO_x in urban areas and all but the most remote rural areas show a marked diurnal pattern of variation consistent with maximum emissions occurring during the morning and evening rush hours when traffic flow is at its highest (Fig. 3.5). Concentrations of NO_2 also show a diurnal pattern, but not as strongly as for NO_x (Fig. 3.5) This reflects the slow conversion of NO in NO_x emissions to NO_2, the influence of other atmospheric reactions on concentrations of NO_2 and the transport of NO_x within air masses.

In urban areas the diurnal variation in concentrations of NO_2 is closely correlated with that of PM_{10}, but the relationship is much weaker in rural areas (Fig 3.6). This is consistent with the importance of traffic and combustion processes in governing concentrations of both pollutants in urban areas. Concentrations of both pollutants in rural areas are substantially affected by photochemical reactions. MAAPE (1995) found that for hourly measurements made between 1992 and 1993 for the then existent urban network, concentrations of NO_2, NO_x, CO and PM_{10} showed varying degrees of positive correlation (Table 3.1). This reflects the overall importance of traffic pollution as sources for these pollutants. The effect was stronger for sites in central urban locations such as London Bloomsbury (MAAPE, 1995) than for the network as a whole. The stronger correlation of PM_{10} with NO_x than with NO_2 reflects the importance of secondary atmospheric reactions in determining concentrations of NO_2, whereas concentrations of NO_x are more closely linked to primary emissions which are dominated by NO.

Table 3.1: Correlations between hourly average pollutant concentrations in the urban network for 1992-1993 based on 75 982 to 100 231 co-located values (MAAPE, 1995)

Pollutant	*NO_x*	*NO_2*	*CO*	*PM_{10}*	*SO_2*
O_3	-0.07	-0.48	-0.45	-0.05	-0.28
NO_x		0.39	0.13	0.80	0.41
NO_2			0.89	0.40	0.70
CO				0.30	0.75
PM_{10}					0.86

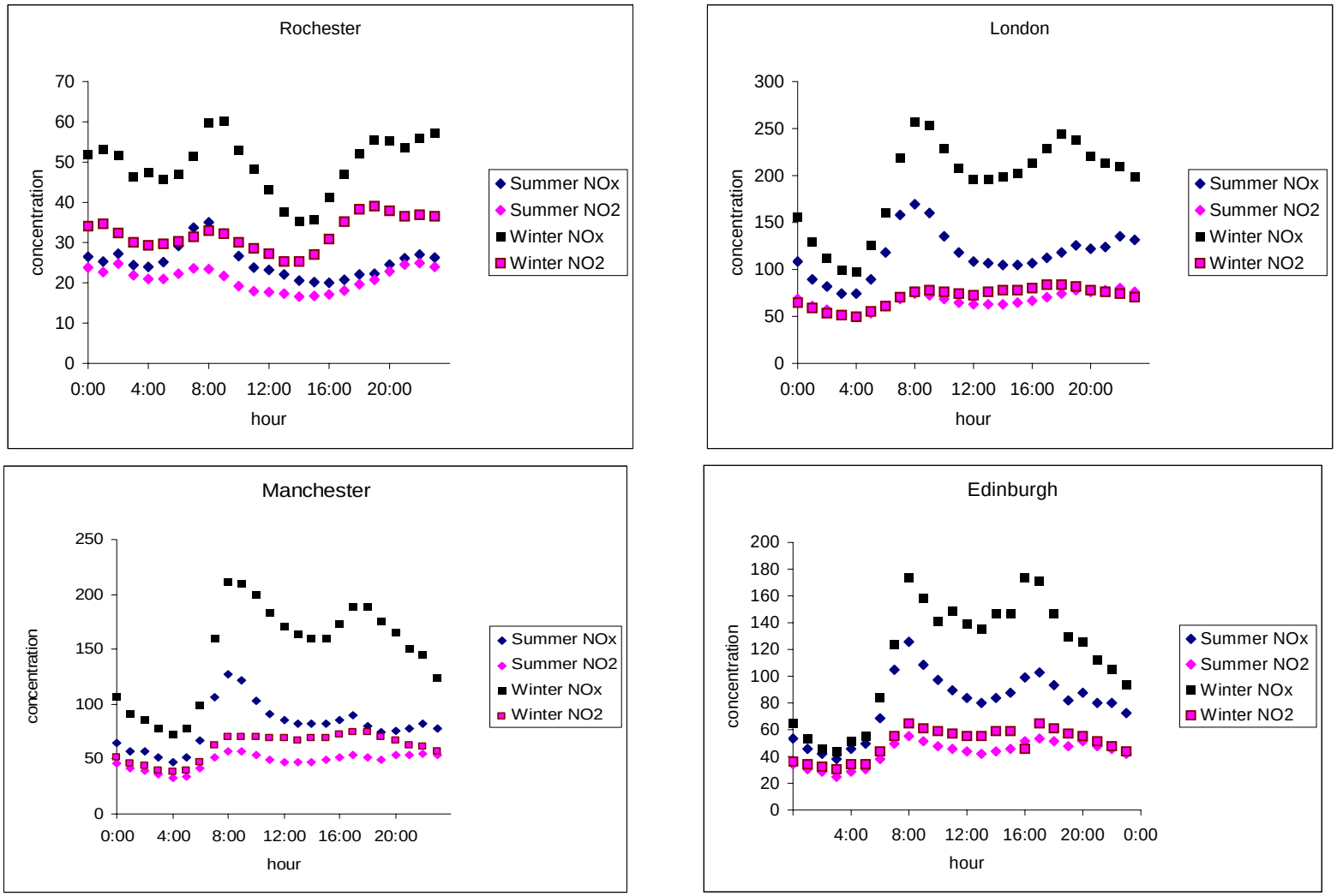

Figure 3.5: Diurnal variation in concentrations of NO_x and NO_2 (μgm^{-3}) at four UK monitoring sites (Rochester is a rural site, the others are urban sites)

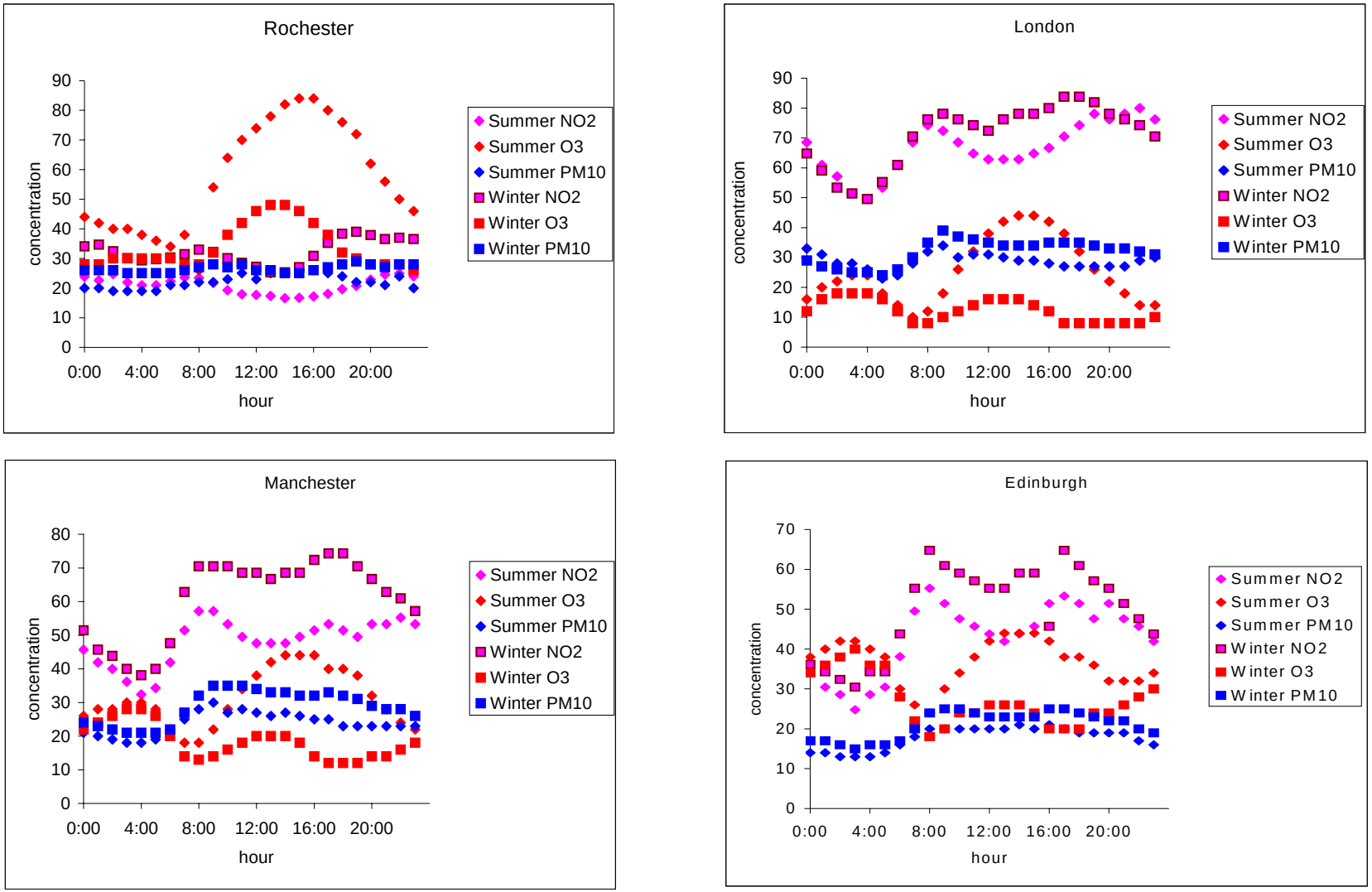

Figure 3.6: Diurnal variation of NO_2, O_3 and PM_{10} (μgm^{-3}) at 4 UK monitoring sites

The diurnal variation in concentrations of NO_2 is generally inversely related to that of O_3 with the relationship being more marked in rural areas (Fig. 3.6). MAAPE (1995) found a significant negative correlation between the hourly mean concentrations of O_3 measured between 1992 and 1993 at a limited number of sites and those of NO_2 or NO_x. These relationships reflect the formation of ozone by scavenging from NO_2 and the development of maximum concentrations of ozone at distance from the source of primary emissions. In terms of the hourly variation in personal exposure to NO_2 and ozone, it is unlikely that individuals within the UK would commonly be simultaneously exposed to elevated NO_2 and ozone concentrations.

Seasonal variation

Mean concentrations of NO_x are higher during the winter months than during the summer in many urban areas within the UK (Figs. 3.6, 3.7). This is presumably due to higher emissions of NO_x and lower levels of ozone formation due to lower temperatures and the reduced intensity and duration of sunlight. Temperature inversions during the winter months may also lead to increased concentrations of NO_x at ground level. There is much less seasonal variation in concentrations of NO_2.

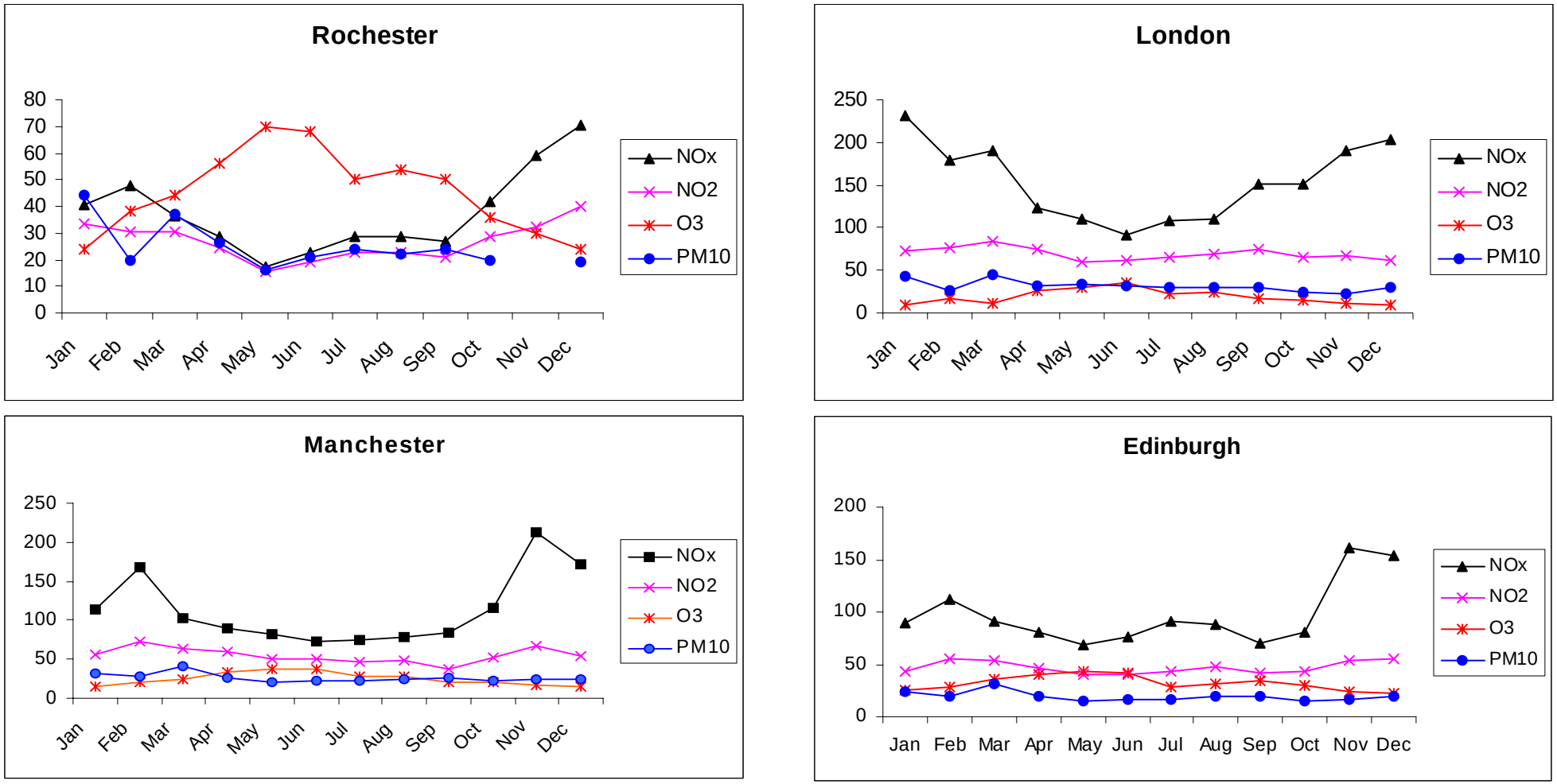

Figure 3.7: variation in monthly mean concentrations (μgm^{-3}) of NO_x, NO_2, ozone and PM_{10} (1996 data)

Relationship between annual mean and peak concentrations of NO_2

The quantification of effects reported in Chapter 8 was based on the annual average concentrations as a measure of exposure to ambient NO_2 (following COMEAP, 1998). This approach assumes that the variability of concentrations is more important than the number of extreme high pollution events. Peak concentrations of NO_2 during high pollution events are correlated with annual mean concentrations such that the use of the annual mean concentration for quantification does capture a large component of the variability in high pollution events in different parts of the UK (Fig. 3.8). If however, the effects of NO_2 are only likely to arise above a certain threshold of exposure, for example, the 1 hour objective, then the annual mean concentration may not provide a reliable indication of the distribution of potential effects in the UK. The number of exceedences of the 1 hour 200 μgm^{-3} standard is only moderately correlated with annual mean concentration (Figure 3.9).

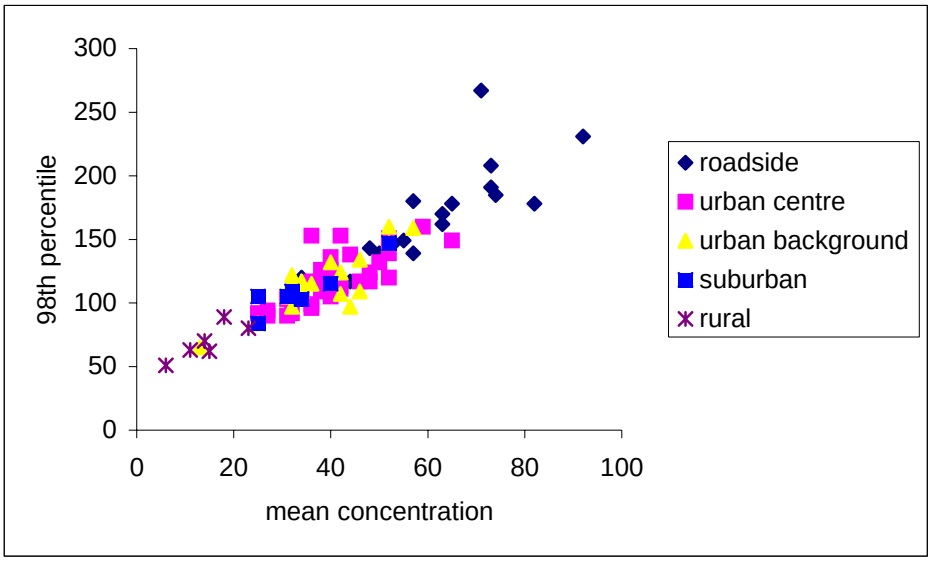

Figure 3.8: Relationship between annual mean concentrations (μgm^{-3}) of NO_2 and the 98th percentile of hourly means (μgm^{-3}) for the UK automatic monitoring network in 1998

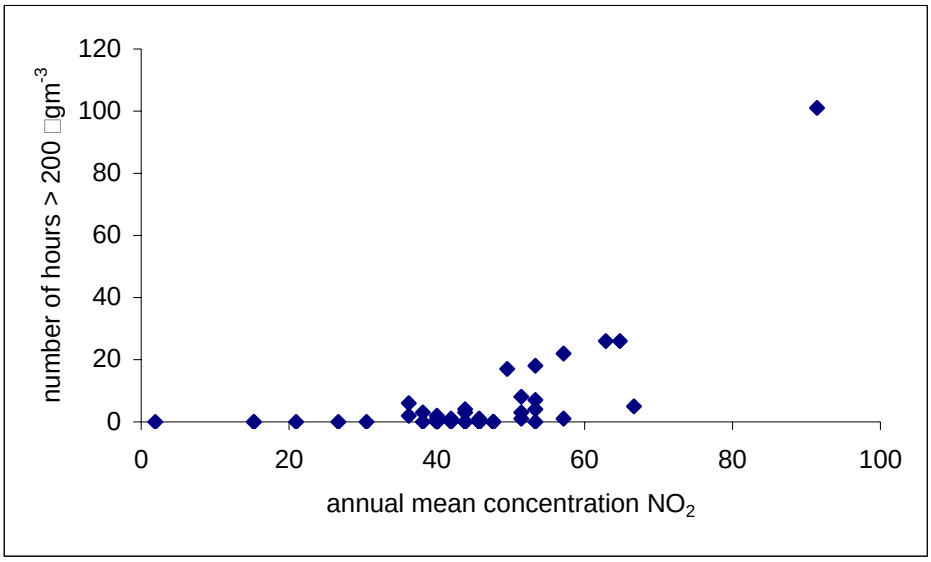

Figure 3.9: Relationship between annual mean concentrations of NO_2 (μgm^{-3}) and the number of exceedences of the 1 hour 200 μgm^{-3} standard for the UK automatic monitoring network in 1996

3.3.3 Ambient concentrations of secondary pollutants formed as a result of NOx emissions in the UK

Ozone

NO_x plays an important role in the formation of ozone during photochemical reactions in the atmosphere (PORG, 1997). Ozone formation is greatest during sunny, summer weather and the rates of formation are such that maximum levels are found 10s to 100s km from the source of emissions. Only a small proportion of the NO_x emitted in the UK contributes to ozone formation in the UK, with 87% of NO_x emissions being exported to mainland Europe (PORG, 1997). Ozone formation in the UK is largely governed by emissions of NO_x in mainland Europe.

Annual concentrations of ozone in the UK range from 18-68 μgm^{-3} (1996 values). Annual mean concentrations are greatest in the most remote and elevated areas of the UK. Concentrations in most urban areas are generally low with the lowest concentrations found at highly polluted sites exposed to NO_x emissions from urban and industrial sources. Ozone is of greater importance in urban areas in the east and south-eastern parts of the country that are subject to VOC emissions from Europe. For example, during 1996 at the Brent monitoring station in London, relatively high concentrations of ozone coexisted with moderate concentrations of NO_x/NO_2 and particulate that are likely to have largely arisen from local traffic emissions.

Peak concentrations of ozone during high pollution episodes range from 48 μgm^{-3} at a kerbside site in central London to 240 μgm^{-3} at a rural site in southern England (97th percentile of daily maximum running 8 hour means, 1998). In recent years, peak concentrations of ozone during high pollution episodes have fallen, although annual mean concentrations have increased (NEGTAP, 2001). The greatest number of short term episodes of high ozone concentrations in the UK occur in southern England, reflecting the importance of ozone precursors arising from Europe and the London conurbation and of high temperatures and sunlight in the formation of ozone.

Reductions in NO_x emissions across Europe would be required to make a substantial difference to ozone concentrations in the UK. A 10% reduction in emissions of NO_x and volatile organic compounds could lead to a reduction in mean ozone concentrations of 4-10 μgm^{-3} (PORG, 1997). This would have little impact on the number of peak ozone episodes that exceed the EPAQS limit, but would be a substantial reduction in long term mean concentrations of ozone. Unilateral measures to cut NO_x emissions in the UK would have little impact on UK ozone concentrations.

Nitrous and nitric acid

Reactions of gaseous NO_x in the atmosphere give rise to nitrous and nitric acid. Concentrations of nitrous and nitric acid vapour are very small (<0.4 μgm^{-3}). Nitric acid (HNO_3) can locally contribute substantially to aerosol acidity, but exists mainly in the gas phase (Wyzga and Folinsbee, 1995). Some combustion processes can lead to the formation of acid coated metallic or soot particles, but historically, NO_x has been of less importance in the development of aerosol acidity than sulphur dioxide. Nitric acid is readily adsorbed by surfaces and tends to be removed rapidly from low level air. Nitrous acid (HONO) can be formed during the use of gas for cooking and heating but is readily decomposed by sunlight.

Aerosol acidity is not measured routinely in the UK. Measurements made in the 1980s in Essex suggest levels of aerosol acidity in Essex were generally between 10 and 20 $nmolm^{-3}$ (equivalent to 0.5-1 μgm^{-3} H_2SO_4) compared with concentrations of about 60-100 $nmolm^{-3}$ measured in Harwell, Oxfordshire (QUARG, 1993). This may reflect both differences in the primary source of sulphur pollution and the availability of ammonia for the neutralisation of acid species formed through photochemical reactions.

Particulate nitrate

Reactions of gaseous NO_x in the atmosphere also lead to the formation of secondary nitrate particles, mostly as sodium nitrate formed by the reaction of nitric acid with sea salt and ammonium nitrate formed by the reaction between ammonia and nitric acid. There is little evidence that photochemical oxidation of NO_x is an important source of secondary nitrate particles (QUARG, 1996). Most secondary nitrate is present within the $PM_{2.5}$ rather than the PM_{10}-$PM_{2.5}$ size fraction (QUARG, 1996).

Soluble particle concentrations are not routinely monitored in the UK (NETCEN, 1998). Concentrations of nitrate of up to 10 μgm^{-3} were measured in rural areas during the 1980s (Table 3.2). Current concentrations are probably considerably lower than during the 1980s, when NO_x emissions were approximately 10 times their present level.

Table 3.2: Measured concentrations of ammonium and nitrate in UK air

		$NH_4^+ \mu gm^{-3}$		$NO_3 \mu gm^{-3}$	
		mean	***range***	***mean***	***range***
Hazelrigg – rural Lancaster 1979-81	24 hour mean concentrations	4.32	0.2-26.2	5.45	0.6-20.2
Essex – mean of four sites	autumn 1986 spring 1987	2.66 5.63		3.07 9.04	

Much less than 20% of NO_x emitted in the UK contributes to the formation of secondary nitrate in UK air (PORG, 1997) and NO_x in air masses originating from mainland Europe has a much greater influence on nitrate concentrations. Modelling suggests secondary particulate formation in the UK is likely to be greatest in East Anglia as a result of primary emissions from mainland Europe. Concentrations in eastern England are likely to be more than double those in remote areas of Scotland and Ireland (QUARG, 1996). Modelling undertaken in the

mid 1990s, suggested that a reduction in nitrate concentrations is likely by 2010 (Table 3.3). More recent modelling suggests that the reduction in UK nitrate concentrations may be as much as 70% by 2010 as a result of reduced NO_x emissions both here and in Mainland Europe.

Table 3.3: Estimated and predicted mean contribution of secondary particles to PM_{10} concentrations in the UK (QUARG, 1996). Typical mean concentrations of PM_{10} are about 20 μgm^{-3}

Contribution	*1995 $PM_{10}\mu gm^{-3}$*	*2010 $PM_{10}\mu gm^{-3}$*
sulphate	2.8	1.2
nitrate	2.9	2.2
ammonium	0.7	0.5
chloride	0.1	0.1
total	6.5	4.0

Secondary organic pollutants

Peroxyacetyl nitrate (PAN) is formed by action of sunlight on VOCs and NO_x but is removed from the atmosphere by thermal decomposition (PORG, 1997). Other organic nitrates are also formed, but at much lower concentrations. Concentrations of the second most abundant homologue – peroxypropionyl nitrate – are only about 10% of those of PAN.

PORG (1997) describe the limited measurement data available for concentrations of PAN in UK air. The average concentration of PAN at Harwell measured between 1987 and 1994 was about 0.175 ppb with daily maximum concentrations of less than 2 ppb. Annual mean concentrations of PAN measured near Edinburgh were 0.15 ppb in 1994 and 0.1 ppb in 1995 with a daily maximum of 1.5 ppb. Average concentrations in Western Ireland during 1995 were 0.03 ppb. Concentrations of PAN were only strongly correlated with those of ozone during photochemical events. During the winter concentrations of PAN exceeding 0.5 ppb were not associated with ozone and generally arose during periods of high pressure weather when easterly winds brought in polluted air from mainland Europe. PAN episodes in Eastern Scotland were generally associated with high pressure weather which brought air from mainland Europe, north over England.

3.4 NITROGEN DIOXIDE IN INDOOR AIR AND RELATIONSHIP TO AMBIENT CONCENTRATIONS

3.4.1 Sources and sinks

Major sources of NO_2 in indoor air include outdoor air, venting of emissions from combustion sources including gas cookers and tobacco smoke (WHO, 1997).

NO_2 is removed from indoor air by absorption onto interior surfaces and furnishings and the formation of nitrous acid on these surfaces. Significant sinks include wallboard, cement block and wool carpet. Sinks of intermediate importance include acrylic or nylon carpets, ceiling tiles, plywood and particleboard. Surfaces with a low capacity to absorb NO_2 include ceramics and glass. Spicer et al (1993) determined the lifetime of trace nitrogen species in indoor environments and found that both nitric oxide and nitrous acid have a lifetime of hours, NO_2 has a lifetime of about an hour, and nitrate has a lifetime of about 30 minutes. Nitrous acid, therefore, may represent a significant fraction of the oxidised nitrogen burden in indoor air. Lee et al (2002) found that in Southern Californian homes, indoor nitrous acid concentrations were closely correlated with indoor NO_2 levels and were about 17% of indoor NO_2 concentrations (9.4 μgm^{-3} compared with 53 μgm^{-3} for NO_2). In comparison outdoor concentrations of nitrous acid and NO_2 were 1.0 and 20 μgm^{-3} respectively. Indoor nitrous acid concentrations were inversely correlated with indoor O_3 levels.

3.4.2 Main influences on indoor concentrations

Many studies have demonstrated that indoor concentrations of NO_2 are influenced by outdoor concentrations (eg Garret et al, 1999; Cyrys et al, 2000), although the effects are generally secondary to those associated with the presence of substantial indoor sources of NO_2 such as gas cooking. Spengler et al (1994) found that in the Los Angeles Basin, 40% of the variation in indoor concentrations could be explained by variations in outdoor levels. Proximity to major trunk roads is an important determinant of concentrations of NO_2 in Japanese homes (Shima and Adachi, 1998).

A large number of studies have established the importance of gas cooking in leading to raised levels of indoor NO_2 (see WHO, 1997 for a review, also individual studies by Alm et al, 1998; Garret et al, 1999; Cyrys et al, 2000; Lee et al, 2002). Other unvented heaters can also give rise to raised levels of NO_2 (WHO, 1997, also Shima and Adachi, 1998, Garret et al, 1999). The influence of gas cooking on indoor NO_2 concentrations is variable and it is apparent that the use of the presence or absence of a gas cooker or other unvented heater is a very crude surrogate for assessing exposure to NO_2 in indoor air (Table 3.4).

Table 3.4: Influence of gas cooking on indoor concentrations of NO_2

Study	***Mean difference (µgm^{-3}) in concentration***		***Comment/ other relevant findings***
	between kitchen with gas cooker and other rooms in same house	***between homes with or without gas cookers***	
Spengler et al (1996)	23	40 vs 13	US, bedrooms, winter
Leung et al (1998)	1.5 times higher		Hong Kong
Gallelli et al (2002)	47 ± 16.5 vs 25 ± 10		
Review WHO 1997	23 (summer 32 (winter)		California
	155		Middlesborough
		42 winter 17 summer	Wisconsin
		30 – 1 heater 50-60 -2 heaters	Connecticut, kerosene heaters

Tobacco smoke is another important influence on indoor concentrations of NO_2 (WHO, 1997, Garret et al, 1999; Alm et al, 1998; Shima and Adachi, 1998; Cyrys et al, 2000). There is little quantitative information about the relative importance of environmental tobacco smoke as a source of NO_2. Effects on NO_2 concentrations would depend on ventilation, room size, number of smokers and number of cigarettes smoked. Samet and Spenglar (1991) refer to a study of office air where tobacco smoke contributed to total NO_2 concentrations of about 46 µgm^{-3}.

Ventilation is important in the exchange of air between the indoor and outdoor environment and in preventing a build up of NO_2 indoors. Several investigators have found that ventilation is a key determinant of indoor NO_2 concentrations (eg Gallelli et al 2002; Cyrys et al 2000). High levels of indoor NO_2 may arise during the winter when the use of heating is greatest and ventilation least (Garret et al, 1999). In the absence of gas cooking, however, ventilation can have the opposite effect, bringing in fresh NO_2 from the outdoor environment. A number of studies have found lower indoor concentrations of NO_2 during the winter than during the summer months.

Overall it is clear that indoor concentrations of NO_2 are very variable. Although gas cooking is an important influence on indoor NO_2 concentrations, the magnitude of effects varies substantially between studies. There are likely to be huge uncertainties in the outcome of epidemiological analyses that have attributed a single value for NO_2 exposure concentrations to approximate the impacts of gas cooking on indoor air quality (eg WHO, 1997). It seems

likely that environmental tobacco smoke is another important influence and its confounding effects on indoor air quality has not been consistently considered in epidemiological studies of the effects of gas cooking.

3.4.3 Relationship between indoor and outdoor concentrations

The WHO (1997) summarise information from an extremely extensive series of investigations of indoor concentrations of NO_2 in the USA. The results of these studies suggest that in homes without gas appliances or unvented heaters, the indoor/outdoor ratio of NO_2 concentrations ranged from 0.27 to 0.97. In homes with gas cookers, the ratio of concentrations in the kitchen to those outdoors was consistently greater than 1.00. The ratio of concentrations in bedrooms to those outdoors was very variable and generally greater than 1. Seasonal effects were highly inconsistent between different areas of the US. For example, in California, the ratio of indoor to outdoor concentrations was highest in the spring and lowest in the winter, whereas in Boston there was little difference between the seasons. A study of homes in the Netherlands with gas cookers reviewed by WHO (1997) found the ratio of concentrations in the kitchen to those outdoors ranged from 1.42 to 3.82. The ratio of concentrations in bedrooms to those outdoors ranged from 0.86 to 2.77. An UK study of homes in Middlesborough with gas cookers reviewed by WHO (1997) found that the mean ratio of concentrations in the bedroom to those outdoors was about 1.7 whereas for kitchens, the ratio was 6.1. Overall, it is apparent that there is substantial variability in the relationship between indoor and outdoor concentrations of NO_2.

3.4.4 Conclusions

Overall, the results of many studies undertaken throughout the developed world suggest that the major influences on indoor NO_2 concentrations are the presence of a gas cooker or other unvented combustion source, smoking, outdoor concentrations and ventilation. The relative importance of these parameters varies between studies, but the most important factor appears to be the presence or absence of a gas cooker. Other factors include ventilation and proximity to traffic. Surprisingly little study has been made of the effects of environmental tobacco smoke on indoor concentrations of NO_2. Outdoor concentrations of NO_2 probably account for less than half of the total variability of indoor NO_2 concentrations. The apparent regional variations in indoor concentrations of NO2 may be largely a function of the selection of properties. The different influences on indoor and outdoor concentrations of nitrogen dioxide mean that it is unlikely that changes in the mean ambient concentration of nitrogen dioxide would be well correlated with changes in the mean indoor concentrations. For example, climatic influences on outdoor concentrations of nitrogen dioxide would influence the extent to which indoor environments are heated or ventilated such that improved dispersion outside might be coupled with poorer dispersion in indoor environments.

There is some doubt about the extent to which measured concentrations of NO_2 in indoor environments are representative of gaseous NO_2 or nitrous acid as standard measurement methods do not distinguish between these two species. Nitrous acid forms from NO_2 in indoor air as a result of reactions on interior surfaces and the lifetime of nitrous acid in indoor air is thought to be longer than that of NO_2. It is therefore likely that the ratio of NO_2 to nitrous acid is greater in indoor air than in outdoor air, although NO_2 is still the dominant species.

3.5 MAIN INFLUENCES ON PERSONAL EXPOSURE TO NITROGEN DIOXIDE

Many studies in both Europe and the USA have found a poor correlation between personal exposure concentrations of NO_2 and ambient concentrations in both adults (eg Gauvin et al, 2001) and children (eg Linaker et al, 2000a). Personal exposure concentrations of NO_2 have been found to be generally higher than ambient concentrations (for example, Monn et al, 1997; Linaker et al, 2000; Liard et al, 1999) although in some studies the converse has been

found (Monn et al, 1998). Most studies of personal exposure concentrations have concluded that concentrations of NO_2 in outdoor air account for less than 50% of the variation in individual exposure concentrations. For example, Spengler et al (1994) reported that 48 % of the variation in personal exposure concentrations in the Los Angeles Basin could be explained by outdoor levels. Liard et al (1999) found that about 41% of the variance in the personal exposure of asthmatic adults could be attributed to outdoor concentrations measured at central locations.

The influence of ambient concentrations of NO_2 on personal exposure appears to be greatest in areas of high traffic flow where local concentrations of NO_2 are significantly raised above background levels elsewhere within the same urban area. A number of studies have found associations between traffic density and personal exposure to NO_2 (eg Rotko et al, 2001; Liard et al, 1999; Gauvin et al, 2001; Rijinders et al 2001). Kramer et al (2000) found that outdoor NO_2 was a good indicator for children's exposure to traffic pollutants but was not predictive of personal exposure to NO_2. Mukala et al (1996) found that the personal exposure of children in Helsinki to NO_2 was significantly greater in the central area than in the suburbs (27.4 μgm^{-3} versus 18.2 μgm^{-3}). This was attributed to the effects of vehicle exhaust. Raaschou Neilson et al (1997) reported preliminary results that suggested that the personal exposure of children in Copenhagen was two or three times higher than in rural districts and that this difference was largely due to differences in ambient levels of NO_2. Similarly, Alm et al (1998) found that personal exposure concentrations of NO_2 for children in Helsinki were 26.5 μgm^{-3} in a downtown area compared with only 17.5 μgm^{-3} in a suburban area. Personal exposure concentrations were much better correlated with concentrations measured inside and outside day care centres than with measurements made at central monitoring site. In general, a poorer correlation would be expected between personal exposure concentrations and ambient concentrations measured at central fixed point monitoring sites than that between personal exposure concentrations and a more local measure of outdoor concentration.

A large number of studies have established that concentrations of NO_2 in indoor air have a major influence on personal exposure concentrations. The presence or absence of a gas stove is a key factor in determining personal exposure (Monn et al, 1998, Levy et al, 1998; Liard et al, 1999; Rotko et al, 2001, Lee et al, 2000, Gauvin et al, 2001, Linaker et al, 1996 and others). Lambert et al (1993) found that for North American infants, their personal exposure concentrations were similar to concentrations in their bedrooms and were heavily influenced by the presence or absence of a gas cooker. Ponsonby et al (2001) found that the greatest influence on children's personal exposures to NO_2 was the use of flued or unflued gas heaters rather than central heating. Environmental tobacco smoke (Rotko et al, 2001, Shima and Adachi, 1998; Pino et al, 1998; Alm et al 1998) and smoking (below) are also important influences on personal exposure to NO_2. Linaker et al (1995) found that children's personal exposure to NO_2 was increased by the use of gas appliances, living with smokers and travel to school by means other than by car. These variables, however, only explained a small part of the total variability. The magnitude of the effects of gas cooking or smoking on personal exposure concentrations of NO_2 has been found to be quite different in different studies. Monn et al (1998), for example, found that for Swiss adults, gas cooking added about 5 μgm^{-3} and smoking about 2 μgm^{-3} to personal exposure concentrations averaging 27 μgm^{-3}. In the absence of gas cooking, ambient concentrations of NO_2 have a more substantial influence on personal exposure. For example, Rotko et al (2001) found that, in the absence of gas cooking, personal exposure concentrations of NO_2 for young adults were significantly associated with home and work location, housing characteristics, traffic volume near home and opening of windows at home.

Lifestyle plays an important role in determining personal exposures to NO_2. Although this would also be true for other pollutants, the influences of lifestyle factors would not necessarily have the same effect as for NO_2. Rotko et al (2001) for example, found that young single adults, those with less education and those in employment tended to have higher levels

of exposure to NO_2 than other individuals. Liard et al (1999) found that age and male sex were also associated with exposure to NO_2 and presumed that this was due to lifestyle factors affecting the amount of time spent indoors and in heavily trafficked areas. Raaschou Neilson et al (1997) found that the personal exposure of Danish children was related to the time spent outdoors and other lifestyle factors including passive smoking and burning candles. Van Wijnen et al (1995) found that personal exposure concentrations were much higher for motorists than cyclists but as cyclists inhaled on average 2.3 time more air than a motorist, their uptake of NO_2 was greater than that of motorists.

Overall, it is clear that personal exposure to NO_2 is not generally strongly correlated in time or space with ambient NO_2 concentrations.

3.6 SMOKING

Tobacco smoke contains a substantial component of NO_2 and the exposure of smokers to NO_2 is likely to be dominated by NO_2 in smoke. Estimates of the quantities of NO_2 inhaled by smokers vary. The WHO (1997) give estimates ranging from 0.079 mg NO_x/ cigarette to 0.73 mg NO_2/ cigarette. For a smoker smoking 40 cigarettes/day, this gives a range of estimated intakes from 3.16 mg NO_x to 29.2 mg NO_2. This compares with a maximum intake from UK urban air of about 1.8 mg NO_2/day and a more typical intake of about 1 mg NO_2/day from urban air. For many smokers, it is likely that their personal exposure to NO_2 is dominated by NO_2 within tobacco smoke.

3.7 CONFOUNDING EXPOSURES

The sources of NO_2 in both ambient and indoor air are also significant sources of fine particulate such that exposures to NO_2 are likely to be correlated with those of PM_{10}, $PM_{2.5}$ and ultrafine particles. Dennekamp et al (2001) report that gas cooking releases substantial amounts of NO_2 and NO (about 1900 μgm^{-3} and 2500 μgm^{-3} respectively over a five minute sampling period), but is also associated with the release of very high levels of ultrafine particles within the size range 15-40 nm. Sarnat et al (2001) found that ambient concentrations of gaseous pollutants such as NO_2 in Baltimore are strongly correlated with personal exposure concentrations for $PM_{2.5}$ suggesting that effects attributed to gaseous pollutants in multicomponent models may actually be due to $PM_{2.5}$. Earlier, however, Sarnat et al (2000) had reported that personal exposure concentrations of $PM_{2.5}$ in older nonsmoking adults in Baltimore are not significantly correlated with NO_2. This may reflect the lower levels of activity of this age group leading to lower levels of exposure to vehicle exhaust or cooking fumes.

A number of epidemiological studies have used NO_2 as a proxy for air pollution more generally, and specifically as an index of traffic related pollution. Ambient concentrations of NO_2 have been found to correlate consistently with the prevalence of reported annoyance related to air pollution and traffic exhaust fumes (Forsberg et al, 1997). In contrast, concentrations of Black Smoke and SO_2 in the same study were not significantly associated with perceived levels of air pollution. Similar effects have been found in relation to indoor air. Koller et al (1993) reported that subjective indicators of well being correlated with objective measures of indoor air quality.

The correlation between NO_2 and ultrafine particles of primary combustion origin is likely to be strongest closest to source. During dispersion, NO_x emissions that are initially dominated by NO are involved in complex photochemical reactions involving ozone and levels of NO_2 slowly increase. Ultrafine particles tend to aggregate to form slightly larger particles. The correlation between NO_2 and ultrafine particles of primary combustion origin is likely to be weakest in areas characterised by high levels of photochemical smog where concentrations of NO_2 would be heavily influenced by photochemical reactions.

3.8 IMPLICATIONS WITH RESPECT TO THE INTERPRETATION OF EPIDEMIOLOGICAL STUDIES

3.8.1 Uncertainties with respect to NO_2 exposure concentrations

The poor correlation between personal exposure to NO_2 and ambient concentrations measured at central monitoring sites is a major problem with respect to epidemiological investigations of the effects of outdoor air pollution. It is not clear that changes in mean ambient concentrations of NO_2 would be reflected in changes in the mean population exposure to NO_2. The influences on personal exposure to NO_2 could even give rise to changes in the population mean exposure that were in the opposite direction to those that might be inferred from measurements made at a central monitoring site. For example, cold windy weather could be associated with increased dispersion of outdoor NO_2 but a build up of NO_2 in indoor environments because of a reduction in the number of open windows. The poor correlation between personal exposure and ambient concentrations of NO_2 is likely to have weakened the power of epidemiological studies to detect effects.

Quantification of exposure is a particular problem in the assessment of the long term effects of exposure to NO_2. The design of cross sectional studies assume stable settled populations with little migration in or out of designated areas. Although, Hoek et al (2001) report that about 90% of a study population was resident at its 1986 address for at least ten years, it seems probable, that populations in many parts of the world, including the UK would be much more mobile. Many studies of indoor air quality have used gas cooking as a measure of NO_2. Given the highly variable impact of gas cooking on indoor air quality and the emission of pollutants other than NO_2, this has weakened the power of these studies to detect health effects that can be attributed to NO_2.

For smokers, the huge effect of smoking on personal exposures to NO_2 is likely to swamp any variability of exposure to ambient NO_2 or NO_2 from other indoor sources. Although most panel studies have specifically excluded smokers, time series and cross sectional studies have generally included the whole population including smokers. Even where studies have excluded smokers, the exposure of nonsmokers to environmental tobacco smoke is highly variable and depends on factors such as whether other people at home or in the workplace smoke and the proportion of time spent in smoky public places such as bars. The effect of smoking is likely to have greatly weakened the power of these studies to detect effects as the day to day or place to place variability in concentrations of NO_2 is so small in comparison to the quantity of NO_2 inhaled by smokers.

3.8.2 Uncertainties with respect to confounding exposures

The co-variation of NO_2 and PM_{10} in ambient air in the UK and elsewhere reflects the importance of combustion sources in determining concentrations of both pollutants. It has led to difficulties in separating the health effects of NO_2 from those of PM_{10} or other measures of particle concentrations in epidemiological studies. Weaker relationships between NO_2 and PM_{10} would be expected where photochemical reactions lead to extensive formation of ozone and secondary particles. It should, therefore, be possible to separate the effects of NO_2 and PM_{10} or $PM_{2.5}$ through the comparison of epidemiological studies undertaken in different locations.

NO_2 has been widely used as a marker of exposure to traffic pollution and it is possible that effects attributed to NO_2 in epidemiological studies are actually caused by either the traffic pollution mix as a whole or some unmeasured pollutant within vehicle exhaust. Several authors have suggested that this unmeasured air pollutant may be ultrafine particles (Seaton personal communication 2003; Wichmann et al, 2000). Both NO_2 and ultrafine particles have common indoor and outdoor sources and concentrations of these pollutants are likely to be

moderately to strongly correlated in both indoor and outdoor air. The relationship between personal exposures to ultrafine particles or NO_2 and ambient concentrations are variable and are affected by factors such as travel to work, cooking and domestic heating. Although it seems likely that individual's personal exposures to ultrafine particles and NO_2 would be highly correlated, the relationship between NO_2 and ultrafine particle concentrations may vary substantially between different microenvironments. It is possible that personal exposures to NO_2 and ultrafine particles are less well correlated for groups of individuals. This variability may be sufficient to allow investigation of the independent effects of personal exposure to NO_2 and ultrafine particles in panel studies where personal exposure concentrations for each pollutant are modelled or measured. More generally, the relationship between concentrations of NO_2 and ultrafine particles would be expected to vary between regions and continents in response to variations in particle origin and atmospheric reactions involving oxidised nitrogen species. It may therefore be possible to separate the effects of ultrafine particles from those of NO_2 in epidemiological studies that embrace areas with very different air pollution characteristics, although there may be difficulties in adequately controlling for differences in other population characteristics.

3.9 IMPLICATIONS WITH RESPECT TO QUANTIFICATION OF THE IMPACTS OF NITROGEN DIOXIDE

The variation in ambient concentrations of NO_2 is unlikely to be strongly associated with most of the sources of variation in personal exposure to NO_2. Most of the sources of variation between the personal exposures of individuals are associated with sources of variation of NO_2 in indoor air and in differences in behaviour with respect to travel, smoking and visits to venues with high levels of environmental tobacco smoke. There is no reason to expect, however, that a rise in ambient concentrations would not have an approximately equivalent incremental effect on personal exposure concentrations for all of the affected population. It may be reasonable therefore to estimate the effects of incremental increases in ambient NO_2 without detailed consideration of personal exposure (see chapter 8). There will, however, be a substantial component of uncertainty arising from the exposure aspect of the quantification because the factors affecting concentrations of NO_2 in ambient air, will have variable effects on personal exposure concentrations.

4. TOXICOLOGY

4.1 INTRODUCTION

Nitrogen dioxide is a reactive compound that can initiate free radical reactions, react with unsaturated fatty acids, induce auto-oxidation of organic compounds and is itself a nitrogen-centred free radical (MAAPE, 1993). Most of the toxic effects of NO_2 are related to its oxidative properties. Its limited solubility means than the absorption and transformation following inhalation is governed by chemical reactions rather than physical dissolution (MAAPE, 1993). It is capable of producing a diversity of nitro-, nitrate or nitroso addition products, as well as other nitrogen oxides or acids and these compounds may have a substantial impact on metabolic and biochemical processes (MAAPE, 1993).

The aim of this chapter is to review the toxicology of NO_2 and assess the implications with respect to the plausibility of the association between NO_2 and adverse health effects reported in some epidemiological studies. This chapter is largely based on earlier reviews by MAAPE (1993), WHO (1997), the American Thoracic Society (1996) and Moldeas (1993). The main health endpoints that are reviewed in this chapter are effects on pulmonary function, immunological response and inflammation in animals. Brief consideration is also given to the uptake and metabolism of NO_2 and the toxicology of closely related compounds including nitric oxide and potential secondary atmospheric pollutants such as nitrous acid and nitrate acid and salts.

4.2 UPTAKE AND METABOLISM

Nitrogen dioxide has a limited solubility in water and the uptake of inhaled NO_2 is governed by reactions with constituents of pulmonary surface lining fluid, a thin layer covering the epithelial cells of the lung which contains surfactant and antioxidants (Putman et al, 1997). The antioxidants glutathione and ascorbic acid are thought to play a key role in the absorption of NO_2 (Velsor et al, 1997). The abstraction of hydrogen ions from organic molecules leads to the formation of nitrous acid and organic radicals (Postlethwaite and Bidani, 1994). NO_2 is only a moderately potent oxidant and whereas compounds with high reactivity such as O_3 react in the upper respiratory tract, compounds with lower reactivity such as NO_2 will penetrate the alveoli (gas exchange region of the lung). A significant amount of inhaled NO_2 is, however, removed in the nasopharynx (about 40-50% in dogs and rabbits). Deposition of NO_2 in the lower respiratory tract is predicted to be greatest at the junction of the connecting airways and the gas exchange region of the lungs in humans, rats, guinea pigs and rabbits. This is where typical NO_2 induced morphometric lesions have been observed in several species following high levels of exposure (WHO, 2001).

The uptake of NO_2 following exposure to high concentrations will be limited by the availability of molecules in pulmonary lining fluid that are able to react with NO_2. The results of experiments with NO_2 and phospholipid monolayers undertaken by Connor et al (2001) suggest that airways surfactant is considerably more resistant to NO_2 uptake than the pulmonary membrane or red blood cells. It is unlikely that NO_2 gas diffuses through the lining fluid to react directly with underlying cells (Postlethwaite and Bidani, 1994).

Experimental studies have shown that NO_2 or its chemical products can remain in the lung for prolonged periods (WHO, 2001). Once absorbed in lung fluids, NO_2 dissolves to form nitrous and nitric acids and both nitrite and nitrate anions are translocated in the blood stream. Mice exposed to high levels of NO_2 (>1000x ambient concentrations) have shown a transient increase in levels of nitrite and nitrate in blood, but concentrations decline rapidly on cessation of exposure. The half life of elimination of nitrite is only a few minutes and that of

nitrate is an hour. It seems likely the effects of inhaled NO_2 would primarily affect the respiratory system.

4.3 LUNG FUNCTION AND BRONCHOCONSTRICTION

The WHO (1997) reviewed a number of studies of the effects of NO_2 on lung function in animals (Table 4.1). The results of these studies suggest that effects depend on both the concentration and duration of exposure and peak exposures substantially increase effects above those associated with continuous exposure to lower concentrations.

Table 4.1: Lung function - summary of findings of animal studies reviewed by WHO (1997)

Concentration µgm^{-3}	*Duration*	*Species*	*Effect*
367 base 1500 peak	23 hour/day 32 weeks 1 hour twice/day	mouse	Decrease in FVC, not observed in absence of daily spikes in concentration
940 base 2820 peak	3 weeks as above 6 weeks as above	mouse	Increased lung volume and compliance in neonates No effects in neonates or adults
3760 base 11300 peak	6 weeks as above	rat	Decreased body weight and lung compliance in adults
940 base 2820 peak	(22 and 2 hours) 52 weeks (22 and 2 hours) 78 weeks	rat	No effects Decreased FEF_{25} and frequency of breathing
3760	8 hours/day, 5 days/week 8 weeks	hamster	No effects
10200	3 hours/day for 7 days	rat	Tendency towards increased lung volumes

There has been little further information published since the WHO (1997) review. Tepper et al (1993) exposed rats for 78 weeks to concentrations of NO_2 of 940 µgm^{-3} with a daily peak of 2820 µgm^{-3} to simulate urban pollution. Lung function tests showed a reduction in ΔFEF25% (Forced Expiratory Flow), a reduced breathing frequency and tidal volume, increased expiratory resistance, and increased inspiratory and expiratory times. No effects were found following shorter periods of exposure. Kobayashi and Miure (1995) exposed guinea pigs to concentrations of 113-7520 µgm^{-3} NO_2 and found a concentration and time-dependent increase in specific airway resistance.

Several investigators have examined the effects of NO_2 on bronchial responsiveness and bronchoconstriction. Chitano et al (1995, 1996) reported that concentrations of 4700 µgm^{-3} had no effects on airways smooth muscle from the main bronchi of guinea pigs and no increase in airways muscle responsiveness was found in rats exposed to 18800 µgm^{-3} for 7 days. In contrast, Papi et al (1999) demonstrated that a four hour exposure to 33840 µgm^{-3} led to bronchopulmonary inflammation and airway smooth muscle hyperresponsiveness in guinea pigs. There was a significant increase in eosinophils and neutrophils in bronchoalveolar lavage fluid, microvascular leakage in the trachea and main bronchi and significant *in vitro* hyperresponsiveness to acetylcholine but not histamine. Halinen et al (2000) reported that bronchoconstriction in guinea pigs exposed to 1880 µgm^{-3} NO_2 was greatest during the first 10 minutes of exposure and was subsequently much reduced. Tidal volume was progressively reduced over a one hour exposure when administered in cold air, but not when administered in warm moist air. Marthan et al (1996) found a dose-dependant increase in human bronchial smooth muscle responsiveness after *in vitro* exposure to NO_2. The alteration in smooth muscle excitation-contraction coupling was associated with indirect effects on neural endopeptase activity. Lucchini et al (1996) also found evidence for the release of neuropeptides by the sensory nervous system on exposure to NO_2. Overall the information suggests that measurable effects on lung function and bronchoconstriction have only been

found in animal experiments at concentrations of NO_2 that exceed 1500 μgm^{-3}. Short term peaks in concentration may have a much greater influence on observed effects that might be anticipated from simple dose comparisons. There is limited evidence to suggest that the airways may adapt to continuing NO_2 exposure in short term experiments with effects on bronchial muscle responsiveness being greatest during the first few minutes of experimental exposure. The results of long term experiments suggest that for a given concentration, effects increase with increasing duration of exposure.

4.4 OXIDATIVE DAMAGE

Many of the adverse effects associated with exposure to NO_2 have been attributed to its oxidant activity. The mediation of NO_2 absorption by glutathione and ascorbic acid pulmonary lining fluid leads to the production of the reactive oxygen species O_2* and hydrogen peroxide (Putman et al, 1997). Levels of antioxidant in the lining fluid are much higher than in plasma and antioxidants play a key role in defending airways epithelial cells from the effects of inhaled oxidants (Kelly et al, 1996). The layer of lining fluid is thickest in the upper airways where it contains high levels of antioxidants and the upper airways are not particularly vulnerable to oxidant injury. It is much thinner and contains fewer antioxidants in the lower airways leading to a much greater vulnerability to oxidant injury.

Lipid peroxidation is believed to have a major role in the toxicity of NO_2 (WHO, 1997). The effects of lipid peroxidation include changes in pulmonary surfactant and membrane fluidity and may ultimately give rise to cellular lesion. Oxidation of the fatty acids of surfactant phospholipids occurs at relatively low levels of exposures and impairs their adsorption to the air-liquid interface. Oxidative degradation of surfactant also results in reduced pulmonary clearance rates and increased retention of inhaled particles (Pdogoski et al 2001). The products of oxidation may promote airways inflammation and oedema (Putman et al, 1997). Table 4.2 summaries the results of experiments with rats reviewed by WHO (1997). Although there are inconsistencies between studies, effects appear to increase with concentration and are enhanced by vitamin E deficiency. The results of experiments with guinea pigs suggest that effects are also enhanced by vitamin C deficiency. The lowest concentration associated with observed effects was 75 μgm^{-3}. In addition to direct oxidative damage, NO_2 may also impair the regulation of surfactant phospholipid metabolism with effects evident in rats at concentrations of 9400 μgm^{-3} following 48 hours exposure (Mengel et al, 1993).

Table 4.2: Lipid peroxidation – summary of results of animal studies reviewed by WHO (1997)

Concentration μgm^{-3}	***Duration***	***Effects***
75	Continuous, 27 months	No effects
752	Continuous, 18 months	Increased lipid peroxidation
7520	Continuous, 9 months	Increased lipid peroxidation
75	Continuous, 9 months	Increased lipid peroxidation
752	6 months	No effects
752	2 weeks	Increased lipid peroxidation
752-7520	4 months	Concentration dependant lipid peroxidation
1880	4 hour/day for 6 days	Lipid peroxidation inhibited by vitamin E supplementation
5640	7 days	Lipid peroxidation enhanced by Vitamin E deficiency

The WHO (1997) also reviewed a number of studies of the effects of NO_2 on antioxidant activity in the lung (Table 4.3). The lowest concentration at which effects on antioxidant activity have been reported is 752 μgm^{-3}. There is no evidence of cumulative effects.

Table 4.3: Oxidative damage – summary of results of animal studies investigating antioxidant activity reviewed by WHO (1997)

Concentration µgm^{-3}	*Duration*	*Species*	*Effects*
75	Continuous, 18 months	rat	No effects
752-7520	Continuous 9 or 18 months	rat	Decreased GSH activity, increased NPSH, no effect on SOD
752-7520	4 months	rat	Concentration dependent increase in antioxidant enzymes, peaking at 4 weeks into exposure
752	2 weeks	Rat Guinea Pig	No effects

A number of more recent studies have investigated the effects of NO_2 on oxidant and antioxidant activity. Van Bree et al (2000) exposed rats to 20 000 µgm^{-3} NO_2 for 4 days (continuous exposure), and found that there was a significant reduction in the activities of antioxidants in lung tissue. Kienast et al (1994) demonstrated that exposure of human alveolar macrophages to NO_2 at concentrations of 118-840 µgm^{-3} for 30-150 minutes yielded a dose-dependent stimulation of reactive oxygen intermediates. Tu et al (1995) found that NO_2 caused a dose-dependent depletion of both glutathione and ascorbate in human epithelial cells. Takahashi et al (1997) reported that exposure to NO_2 activated glutathione metabolism in the lung with effects found in both lung tissue and lavage fluids. Pagini et al (1994) found that in exposure of rats to 9 mgm^{-3} NO_2 or 18 mgm^{-3} NO_2 for 24 hours gave rise to an increase in total glutathione levels in blood whereas oxidised glutathione levels were not affected. Kelly et al (1996) reported a differential consumption of antioxidants with uric acid being consumed first, then ascorbic acid and then glutathione. Robison et al (1996) suggested that the pulmonary injury caused by NO_2 may partly arise as a result of the generation of aldehydes that bind cellular proteins and subsequently impair or inhibit cell function. Guinea pig epithelial cells exposed to NO_2 were found to generate higher than normal levels of glycolaldehydes.

In conclusion, exposure to concentrations of NO_2 that are similar to ambient concentrations during high pollution events has been found to cause oxidative damage to airways surfactant in animals. This in turn may adversely affect clearance and lung function. Levels of antioxidant activity within lung lining fluid have an important influence on susceptibility to oxidant induced damage suggesting that diet may play a role in governing susceptibility to the adverse effects of oxidant gases. It seems plausible that oxidant damage to airways surfactant may play a role in the association between NO_2 and adverse health effects observed in epidemiological studies.

4.5 INFLAMMATORY RESPONSE

Inflammation in animal experiments is normally assessed from changes in the cell counts and concentrations of various enzymes and proteins in bronchioalveolar lavage (BAL) fluids. Exposure to NO_2 is associated with inflammation of the lung marked by infiltration of serum protein, enzymes and inflammatory cells and hyperplasia of type 2 epithelial cells (WHO, 1997). Exposure of nasal or bronchial epithelial cells to NO_2 results in the synthesis and release of pro-inflammatory mediators including eicosanoids, cytokines and adhesion molecules (Devalia et al 1997). Airways epithelial cells respond to oxidants by activation of transcription factors such as nuclear kappa B resulting in increased transcription of genes for certain cytokines such as interleukin 8 and inflammatory enzymes such as inducible NO synthase and cyclooxidase (Barnes, 1995). Table 4.4 summarises the findings of some of the studies reviewed by the WHO. Most of these experiments investigated relatively high levels of exposure. The lowest level associated with adverse effects was 752 µgm^{-3} in vitamin C deficient animals. The lowest level at which effects were observed in other animals was 1880 µgm^{-3}. There is limited evidence to suggest that the lung adapts to continuing NO_2 exposure

leading to the resolution of inflammation developed during the early weeks of experiments. Gregory et al (1983) report that lung lavage fluids recovered from rats exposed to 1905 μgm^{-3} with two daily spikes of 9525 μgm^{-3} or 9525 μgm^{-3} for 7 hours/day, 5 days/week for up to 15 weeks showed evidence of an inflammatory response including increased levels of lactate dehydrogenase (indicative of cell death). After 15 weeks of exposure, all biochemical markers of inflammation had resolved, although the histopathological changes observed were more permanent (see below).

Table 4.4: Inflammatory response – summary of results of animal studies reviewed by WHO (1997)

Concentration μgm^{-3}	***Duration***	***Species***	***Effects***
75	Continuous for 9 or 18 months	rat	No effects
752	72 hours	Guinea pigs	No effects
1880	72 hours	Guinea pigs	Increase in BAL protein in vitamin C deficient animals
1880-9400	15 weeks	rats	Changes in BAL and tissue enzyme activity resolved by 15 weeks
3760	1-7 days	rats	Increased lung protein content
9400-47000	Continuous 7 days	rats	Increased rate of collagen synthesis

A number of further experimental studies have undertaken since the WHO review (Table 4.5). The lowest concentration associated with observable effects has been 1800 μgm^{-3}. Lehnert et al (1994) demonstrated that, at higher concentrations, effects scaled with mass concentration and that concentration was more important than exposure time in determining effects. They also found that exercise following exposure to NO_2 can greatly enhance the extent of lung injury.

Table 4.5: Inflammatory response – summary of results of more recent studies

Concentration µgm^{-3}	*Duration*	*Species*	*Effects*	*Reference*
5640 µgm^{-3}	6 hours/day, 6 days/week for 2 weeks	guinea pigs	decreased ciliary activity, slight eosinophil accumulation on the epithelium and submucosal layer of the nose	Ohashi et al (1993)
16920 µgm^{-3}			more severe epithelial injury and prominent eosinophil influx	
9000 µgm^{-3}	24 hours	rats	significant increase in polymorphonuclear leukocytes in bronchiolavage fluid	Pagini et al (1994)
9000 to 18000 µgm^{-3}	7 days		significantly increased number of macrophages in BAL fluids, inhibition of ex vivo phorbol myristate acetate-induced superoxide anion production, dose and time dependent increase in alpha 1-proteinase inhibitor	
18800 µgm^{-3}	7 days	rats	influx of macrophages into the airways, increase of inflammatory markers in the respiratory bronchioles and alveoli, loss of cilia in the small airways.	Chitano et al (1996)
1880 µgm^{-3}		guinea pigs	increased proportion of macrophages in BAL fluids, when the NO_2 was administered in cold air	Halinen et al (2000)

Overall it is clear that exposure to high concentrations of NO_2 can induce an inflammatory response in the airways. Effects have only been found, however, at concentrations of NO_2 that greatly exceed those in ambient air. There is limited evidence to suggest that the inflammatory effects of NO_2 are enhanced by cold dry air. There is also limited evidence to suggest that the inflammatory response to moderate concentrations of NO_2 gradually resolves during continuing exposure.

4.6 EFFECTS ON AIRWAYS DEFENCE FUNCTIONS

4.6.1 Mucociliary clearance

Airways mucus

The clearance of foreign bodies from the airways involves phagocytosis by alveolar macrophages and the transport of material in the mucociliary escalator. The mucus that coats the airways plays a key role in protecting the cells lining the airways and in facilitating mucociliary clearance. Inhalation of NO_2 leads to mucus hypersecretion and altered mucus rheology (Samet and Cheng, 1994). This affects lung clearance and respiration.

Ohashi et al (1994) examined the effects of NO_2 on the mucosa of the guinea pig nose and found that exposure to concentrations of 5715 µgm^{-3} caused decreased ciliary activity and slight eosinophil (inflammatory cell) accumulation in on the epithelium and submucosal layer. They suggested that this could contribute to hyper responsiveness and the development of allergic rhinitis. In a follow-up study (Ohashi et al, 1998), they were able to demonstrate that

exposure of guinea pigs to high concentrations of NO_2 could trigger allergic hyper responsiveness.

Alveolar macrophages

Alveolar macrophages play a key role in lung clearance and the WHO (1997) reviewed a number of studies of effects of NO_2 on macrophage function (Table 4.6). The results of some of these studies are also relevant to understanding the effects of NO_2 with respect to susceptibility to infection as discussed in more detail below. Effects do not appear to be proportional to concentration or duration of exposure. Some of the study results shown in Table 4.6 suggest that peak exposures may have a disproportionately important influence on effects.

Table 4.6: Changes in macrophage function – summary of results of animal studies reviewed by WHO (1997)

Function	***Species***	***Concentration µgm^{-3}***	***Duration***
Changes in macrophage morphology no effects level	rat	7520	6 hour/day, 7,14 or 21 days
	mouse	940 continuous 3760 2 hr peak	5 days/ week, 21 weeks
		940 continuous 1880 2 hr peak	5 days/week, 24 weeks
Increased numbers of macrophages	rat	1880 base 7 hr 9400 peak1.5hr	5 day/week, 15 weeks
		7520	10 days
Reduced phagocytic activity No effects level	Rat	7520	10 days
	mouse	9400	7 days
Decreased production superoxide anion radical	Rat	2444-31960	
	rat	7520	10 days
Reduced bactericidal activity No effects 5% 35%	mouse	 1880 4320 12400	17 hours

The results of the studies reviewed by WHO (1997) are broadly consistent with those of Hooftman et al (1998) who found that exposure of rats to concentrations of 7620 µgm^{-3} or more for 7 to 21 days gave rise to a change in macrophage morphology. Other effects on macrophages reported by Hooftman et al, however, only occurred at concentrations that are markedly higher than those reported in the studies cited by the WHO. Increased macrophage numbers were observed following exposure to concentrations of 19050 µgm^{-3} for 7 to 21 days and reduced phagocytic capacity was observed following 14 days exposure.

More recently, Van Bree et al (2000) found increased levels of macrophage activity in the lungs of rats exposed to concentrations of 20 000 µgm^{-3} of NO_2 for 4 days (continuous exposure). The recovered macrophages showed no loss of viability or phagocytic capacity when compared to those recovered from unexposed controls. In contrast, when Robison et al (1993) exposed rats to concentrations of 940 µgm^{-3} for 5 to 10 days, they found evidence of a short term reduction in the activation of AM arachidonate metabolism and superoxide production in response to external stimuli. This impairment of normal cellular defence functions may lead to a reduced defence against pulmonary infection.

Macrophage mediated clearance

A number of *in vitro* investigations have looked at specific aspects of macrophage clearance. Devalia et al (1993) exposed human epithelial cells to concentrations of 753 and 1504 µgm^{-3} of NO_2 and found evidence of membrane damage, permeability and attenuated ciliary beat frequency. In contrast Riechelmann et al (1994) found that exposure to NO_2 for 2 hours at

concentrations up to 28 200 μgm^{-3} did not decrease the ciliary beat frequency of cells scraped from the nasal passages of human volunteers. Similarly, Knorst et al (1994) found that the exposure of guinea pig tracheas to NO_2 at concentrations of 5640 to 28 200 μgm^{-3} did not induce any changes in mucociliary activity and ciliary beat frequency.

Two *in vivo* investigations of the effects of NO_2 on particle clearance have been undertaken during the last decade. Kakinoki et al (1998) exposed rabbits to 5640 μgm^{-3} of NO_2 over 24 hours and found that all epithelial defence functions including ciliary activity, mucociliary transport velocity and epithelial permeability were significantly inferior to those in the control group. Only about two thirds of the animals, however, appeared to have been susceptible to the effects of NO_2 at that concentration. They suggested that epithelial dysfunction induced by NO_2 may be involved in the clinical manifestation of airways allergic disorders. Ramussen et al (1994) examined effects of NO_2 exposure on the clearance of tracer particles in ferrets. Particle clearance in ferrets exposed to 18800 μgm^{-3} for 8 or 15 weeks (4 hour/day, 5 day/week) was significantly impaired but there was no difference between the 8 and 15 week groups. There was a nonsignificant reduction in clearance in animals exposed to 940 μgm^{-3}. The impairment of clearance function may be only slowly recovered after chronic exposure. The WHO (1997) reviewed a study in which rabbits exposed to 564 μgm^{-3} or 1880 μgm^{-3} for 2 hours/day for 1 or 14 days showed an increase in alveolar clearance. Mauderly et al (1987) report reduced clearance of diesel soot in adult rats exposed to diesel exhaust containing NO_2 for six months. Similar effects were not seen in juvenile rats exposed to diesel exhaust during development.

Conclusions

Exposure to high concentrations of NO_2 leads to impaired mucociliary clearance but effects have not been demonstrated at ambient concentrations of NO_2. Some damage to airways mucus and cells, that could contribute to impaired clearance, has demonstrated at concentrations of NO_2 that are 5 to 10 times greater than peak ambient concentrations. Young animals do not appear to be more susceptible to effects than mature animals.

4.6.2 Interaction with infectious agents

Several authors have suggested that NO_2 may increase susceptibility to respiratory infections but the results of cellular and animal investigations of immune function do not provide a clear picture. In 1993, MAAPE noted that many of the studies that were available for review had been undertaken at concentrations of NO_2 that cause significant toxicity in the absence of infection. Other studies had exposed animals to such high levels of the infectious agent that up to 40% of animals who had not been exposed to NO_2 died. Few investigators had used morbidity as an end-point or investigated near ambient concentrations of NO_2. In addition susceptibility to bacterial infection has a considerable genetic component. Despite these short comings, MAAPE concluded that the results of available studies demonstrated that exposure of mice to concentrations of NO_2 of 940 to 1880 μgm^{-3} increased susceptibility to viral infection. High concentrations of NO_2 (7100 μgm^{-3}) had more effect on susceptibility to infection if exposure immediately followed bacterial challenge than if it preceded the challenge. The increased susceptibility to infection might arise through alteration of alveolar macrophage function.

WHO (1997) reviewed a large number of studies of the effects of NO_2 on susceptibility to bacterial infection (Table 4.7). Effects were seen following repeated exposures to concentrations of as low as 940 μgm^{-3} over 3 months (time averaged concentration equivalent to only 117 μgm^{-3}). The lowest concentration associated with effects following a single acute exposure (4 hours) was 1880 μgm^{-3}. No effects were observed at 100 μgm^{-3}. There was limited evidence that peak concentrations of exposure had a more important influence in reducing resistance to infection than cumulative exposure. This implies that long term low

level exposure to NO_2 may not lead to progressive damage to bacterial defences, whereas short term high level exposures may exceed a threshold, above which impairment of bacterial defences is initiated. There is also very limited evidence that duration of exposure influences effects, but duration would be appear to be of much less importance than exposure concentration. The results of other studies suggest that duration of exposure has no significant impact on effects. The WHO (1997) also reviewed susceptibility to viral infection (Table 4.8). Much less information was available than for bacterial challenge but the lowest level associated with effects in mice was similar to that observed with bacterial challenge. Studies published since the WHO review provide little further information. The results of experiments with epithelial cells undertaken by Becker and Soukup (1999), for example, suggest that NO_2 did not increase the susceptibility of these cells to viral infection. NO_2 did, however, reduce the efficiency of cellular defences that would normally prevent the spread of the virus such as the release of virally-induced cytokines. More recently Koike et al (2001), found that in rats exposed to concentrations of 1880 μgm^{-3} NO_2 for 3, 14 or 28 days, there was an inhibition of alveolar macrophage immunosuppressive activity through the inhibition of nitric oxide production. Effects increased with increasing length of exposure. Dandrea et al (1997) investigated the release of cytokines from human alveolar macrophages from smokers and nonsmokers. The results suggested macrophage derived cytokine mediators of the sepsis response may not play a role in the generation of NO_2 induced inflammation in the human lung. The gas seemed to non-specifically inhibit the release and/or production of cytokines, particularly from smokers' cells at the post-transcriptional level and to impair the ability of the cells to increase the transcription and release of cytokines in response to bacterial lipopolysaccharide. The fact that NO_2 seriously impaired the already diminished capacity of smoker's cells to release several important pro-inflammatory cytokines suggests that the inhalation of NO_2 in cigarette smoke may contribute to impairing host defence against infection in the lung. Overall, it appears that NO_2 may impair defence against infection at concentrations similar to the peak concentrations that may arise in ambient air.

Table 4.7: Susceptibility to bacterial infection – summary of results of animal studies reviewed by WHO (1997)

Concentration µgm^{-3}	*Duration*	*Species*	*Effect*
100 continuous 188 peak	5 days/week, 15 days	Mouse	No effects
940 continuous 1880 peak			Increased mortality
376 continuous 1500 peak 1 hr/twice daily	5 days week, one year	Mouse	Increased mortality in group exposed to spike
940	3 hr/day, 3 months	Mouse	Increased mortality
1880	17 hours	Mouse	No effects
4320 12400			Increased mortality
1800-4700	4 hour	mouse	Impaired bactericidal activity
1880	3 hours	mouse	No effects
5640			Increased mortality
2820	Continuous 7 days 7 hrs/day 7 days	mouse	Mortality increased following continuous rather than intermittent exposure
2820	Continuous 14 days 7 hrs/day 14 days	mouse	No significant difference between continuous and intermittent exposure
8460	1, 3.5, 7 hours	mouse	Mortality increased in proportion to duration of exposure for immediate but not a delayed bacterial challenge
9400	2 months	Squirrel monkey	Increased mortality
 13160 17300 27800	4 hour	mouse	Reduction in bactericidal activity 7% 14% 50%

Table 4.8: Viral infectivity – summary of results of animal studies reviewed by WHO (1997)

Concentration µgm^{-3}	*Duration*	*Species*	*Effects*
940-1880	Continuous for 3 days	Mouse	Increased susceptibility to infection
1880	2 hours	Mouse	Increased susceptibility to infection
9400	Continuous for 2 months	Squirrel monkey	Increased viral induced mortality

4.6.3 Humoral and cell mediated immunity

The WHO (1997) reviewed a number of studies, some of which are summarised in Table 4.9. The results of these studies show some inconsistencies. The lowest levels of exposure associated with possible effects on cellular immune function is 188 µgm^{-3} coupled with a daily peak exposure concentration of 470 µgm^{-3}. Effects were also observed with exposure concentrations of 470 µgm^{-3} for 7 hours a day (equivalent to a time averaged concentration of 120 µgm^{-3}). The absence of other studies reporting effects at concentrations below 200 µgm^{-3} suggests that the peak exposures may have had an important influence on the experimental outcome. Although the studies generally suggest that NO_2 is associated with depression of immune functions, the experimental results suggest that low level exposure may stimulate the response of some components of the immune system to challenge.

Table 4.9: effects on humoral and cell mediated immunity – summary of results of animal studies reviewed by WHO (1997)

Concentration µgm^{-3}	*Duration*	*Species*	*Effects*
188 base 470 peak (3hr)	5 days/week, 6 months	mouse	Suppression of splenic T and B cell responsiveness to mitogens
470	7 hours/day, 7 weeks	mouse	Reduced total T cell population
752	Continuous, 4 weeks	mouse	Decrease in primary plaque forming cell response
940 base 3760 peak (1hr)	5 days/week, 3 months	mouse	Decreased serum IgA, increased IgG, IgM
1880	493 days	monkey	Earlier and greater increase in serum neutralisation antibody tires to monkey-adapted influenza
1880	6 months	Guinea pig	Decreased haemolytic activation of complement following challenge with K pneumoniae
9400	169 days	monkey	Initial depression in serum neutralisation titres
9400	6 months	monkey	Depressed serum antibody formation
9400	24 hours	rat	Concentration dependent elevation of cellular immunity following immunisation with sheep red blood cells

Since the WHO (1997) review, a number of other studies have investigated the effects of NO_2 on allergic reactions. Gilmour et al (1996) found that the exposure of rats to concentrations of NO_2 of 9400 µgm^{-3} after both immunisation and challenge with dust mite allergen was associated with significantly higher levels of antigen specific IgE, local IgA, IgG and IgG antibodies. They also found an increased number of inflammatory cells in the lungs and increased lymphocyte responsiveness to antigen in the spleen. Kitabatke et al (1995) exposed guinea pigs to concentrations of 9400 µgm^{-3} of NO_2 for 4 hours/day for 5 days/week for six weeks and found an increased reaction to *Candida albicans* including an increase in delayed type dyspnoea. Siegel et al (1997) exposed rats to extremely high concentrations of NO_2 (163560 µgm^{-3}) for 1 hour and found increased IgE, IgG and IgA responses to ovalbulmin together with increased cell counts in bronchioaveolar lavage fluids. Ohashi et al (1998) found that exposure of guinea pigs to nitrogen dioxide led to an accumulation of eosinophils in the epithelium of the trachea and had a massive effect on the reaction between antigen and antibody following sensitisation. They suggested that although NO_2 does not cause substantial epithelial injury in isolation, it could be a trigger for hyper responsiveness in allergic airways and is probably involved in the pathogenesis of airway allergic disorders. A review by Wallaert et al (1998) concluded that exposure to NO_2 enhances the formation of allergen dependent IgE and, following sensitisation, NO_2 leads to an increased response to allergens. Overall, the results of animal experiments are consistent with an association between NO_2 and enhanced allergic reaction to other substances, but reported effects are found at concentrations of NO_2 that are much greater than those found in ambient air.

4.7 EPITHELIAL CELL CHANGES INCLUDING PROLIFERATION

There is an extensive literature describing the effects of exposure to NO_2 on airways epithelial cells. Different species have different levels of susceptibility to effects (MAAPE, 1993). The WHO (1997) reviewed both short to medium term (Table 4.10) and long term (Table 4.11) studies. The results of the short to medium term studies are inconsistent. The lowest level at which effects have been observed is 639 µgm^{-3} while other studies have found no effects at concentrations of 3760 µgm^{-3}. There is no clear evidence of interspecies differences in susceptibility to the effects of NO_2. Generally, concentration appears to be a more important determinant of effects than duration of exposure, but some individual studies have shown a

progressive increase in effects with increased time of exposure. The results of longer term studies suggest that prolonged exposure of rats to concentrations of 940 μgm^{-3} can give rise to epithelial type 2 cell hyperplasia, although no effects were seen in monkeys following prolonged exposure to 1880 μgm^{-3}. The results of another study not reviewed by WHO (Gregory et al, 1983) reported histopathological changes in some rats exposed to 1905 μgm^{-3} with two daily spikes of 9525 μgm^{-3}, or 9525 μgm^{-3} continuously, for 7 hours/day, 5 days/week for 15 weeks. Changes included focal areas of hyper inflammation and alveolar macrophage accumulation. There is limited evidence from the studies reviewed by WHO to suggest that the effects of continuous exposure to a given concentration are greater than following exposure for only part of each day. There is also limited evidence that effects associated with any given concentration increase slightly with duration of exposure, although concentration is the more important determinant of effects. The results of other studies reviewed by WHO (1997) suggest that neonates are relatively resistant to the effects of NO_2 prior to weaning and that responsiveness increases subsequent to weaning. The susceptibility of mature animals appears to decline with age, but then increases in older animals.

Table 4.10: Effects on cell proliferation – summary of results of short-term animal studies reviewed by WHO (1997)

Concentration μgm^{-3}	*Duration*	*Species*	*Effects*
207-16500	1 month	rat	Various morphological changes
639	6 hours/day, 5 days/week, 6 weeks	mouse	Type 2 cell hypertrophy and hyperplasia
940	4 hours 6 days	rat	Loss of cytoplasmic granules in and rupture of mast cells Increased numbers of mast cells
940 base 2820 peak	Continuous 6 weeks 1 hr twice daily	rat	Increased area covered by Type 2 cells, Type 2 cell hypertrophy, increased alveolar macrophages
1000	90 days	Guinea pig, rabbit, dog, monkey, rat	No pathology
1320-1500	1 month	mouse	Hypersecretion of mucus, focal degeneration and desquamation of mucous membrane, terminal bronchial epithelial hyperplasia, some alveolar enlargement, shortening of cilia
1880	1 month	mouse	Terminal bronchiolar epithelial hyperplasia
1880	1 hour	rat	Degranulation and decreased numbers of mast cells
2500	28 days	rat	No pathology
3700	3 days	Rat Guinea pigs	No histological changes Thickening of alveolar walls, oedema, increase alveolar macrophage numbers, loss of bronchiolar cilia
5000	28 days	rat	Thickening of centriacinar septa within 2 days, loss of ciliar, abnormal ciliar in trachea and main bronchi within 4 days, hypertrophy of bronchiolar epithelium within 8 days
9400	90 days	monkey	Bronchiolar epithelial hyperplasia, some focal oedema

Table 4.11: Effects on cell proliferation – summary of results of long-term animal studies reviewed by WHO (1997)

Concentration μgm^{-3}	*Duration*	*Species*	*Effects*
75 752	27 months 18 months	rat	No effects Slight increase in air-blood barrier
940	4 months	rat	Hypertrophy of epithelial type 2 cells and interstitial oedema
940	7 months	rat	Swelling of terminal bronchiolar cilia and hyperplasia of epithelial type 2 cells
1500	lifetime	rat	Minimal changes, slight enlargement of alveoli and alveolar ducts
1880	7 hr/day, 5 days/week, 15 weeks	rat	No pathology
1880	6 hr/day, 5 days/week 6 months 12 months 18 months	dog	 No effects Dilated alveoli and alveolar ducts Dilated alveoli, oedema, thickened alveolar septa
1880	7 months	rat	Cilia loss in terminal bronchioles, hyperplasia of epithelial type 2 cells, interstitial oedema
1880	16 months	monkeys	No pathology
3760	14 months	monkeys	Bronchiolar epithelial hypertrophy
7520	9 months	rat	Hypertrophy and hyperplasia of bronchiolar epithelium

There have been a number of recent investigations of the effects of NO_2 on epithelial cells. Van Bree et al (2000) exposed rats to 20 000 μgm^{-3} NO_2 for 4 days (continuous exposure), and found that there was extensive modification of the appearance of Type II epithelial cells. These developed a squamous, less cuboidal appearance than those in unexposed animals. Barth and Muller (1999) exposed rats to concentrations of 9400 to 37600 μgm^{-3} of NO_2 for 3 and for 25 days. After 3 days exposure to 9400 μgm^{-3}, there was clear evidence of damage to epithelial cells including significant alteration of cell morphology and increased rates of cellular proliferation. After 25 days, rates of epithelial proliferation had reduced to the levels found in controls and the morphology of epithelial cells was indistinguishable from that found in controls. This was interpreted to reflect adaptation to oxidative stress. Long term exposure to 18800 or 37600 μgm^{-3}, however, led to a dose dependent increase in cell proliferation in the bronchial and bronchiolar epithelium. Robison and Kim (1995) found that guinea pig tracheobronchial epithelial monolayers exposed for 1 hour to concentrations of NO_2 of 3760 μgm^{-3} showed a significant increase in permeability. Exposure to 1800 μgm^{-3} was sufficient to cause a significant increase in ion transport through cells. These results suggest that even short term exposure to slightly elevated levels of NO_2 could affect the barrier function of airways epithelium giving rise to increased levels of transport of ions and fluid through the epithelium. Ramussen (1994) demonstrated that chronic exposure of experimental animals to moderate levels of NO_2 leads to increased collagen deposition in the lung parenchyma. Exposure of ferrets to concentrations of NO_2 of 18800 μgm^{-3} for 4 hours/day for 8 of 15 weeks gave rise to a significantly increased level of collagen deposition in lung tissue associated with the respiratory bronchiolar submucosa. Levels of collagen deposition did not reduce after a 7 week recovery period.

Overall, it is clear that exposure to NO_2 can cause extensive damage to lung epithelial cells at concentrations of NO_2 that are much greater than those found in ambient air. There is no

evidence to suggest that processes leading to lung fibrosis are likely to be initiated in response to exposure to ambient levels of NO_2.

4.8 EMPHYSEMA

The WHO (1997) reviewed a number of high dose experiments in which emphysema was induced in animals. Their interpretation was complicated by differences between studies in the definition of emphysema. The WHO concluded that emphysema was only developed in animal experiments at high levels of exposure (Table 4.12). A number of studies found no emphysema in animals exposed for prolonged periods to concentrations of NO_2 that were orders of magnitude higher than those likely to arise in ambient air.

Table 4.12: Emphysema – summary of effects found in animal studies reviewed by WHO (1997)

Concentration µgm^{-3}	***Duration***	***Species***	***Effects***
188 base 1880 2 hr peak	6 months	Mouse	Equivocal emphysema
263 plus 2050 µgm^{-3} NO	16 hr/day, 68 months	Dog	None
1200 plus 310 µgm^{-3} NO			Emphysema
940	12 months	Mouse	None
9400	3 months	Monkey	Equivocal emphysema
9400	Up to 18 months	Dog, rabbit, guinea-pig, rat, hamster, mouse	None
28000	Intermittently for 2 years	Rat	Equivocal emphysema
28000	3-5 months	Rat	none
28200	Continuously for 35 days then intermittently for at least 2 years	Rat	Equivocal emphysema
37600	Up to 33 months	Rat	Emphysema
47000	32-65 days	Rat	None
56400	12 months	Hamster	none
56400	Up to 140 days	Rat	Equivocal emphysema
65800	6 hr/day, 25 days	Rat	none
75200	8 weeks	mouse	none
94000-169000 reduced to 56400 to 94000	2 hours/day, 5 days/week, 12 months	Hamster, guinea pig	Equivocal emphysema
84600-103400	22-23 hours/day, 10 weeks	Hamster	none

Mercer et al (1999) found that the exposure of rats to 0.5 ppm (262 µgm^{-3}) NO_2 with twice daily spikes to 1.5 ppm (785 µgm^{-3}) was associated with the formation of fenestrae through the atrophy of interstitial spaces. The effects were similar to the initial steps in an emphysema-like destruction of alveolar septa. Barth et al (1995) found concentration and time-dependent changes in rat lung tissue consistent with the progressive development of emphysema at relatively high levels of exposure (Table 4.13).

Table 4.13: Summary of results of experiments in rats undertaken by Barth et al (1995)

Duration µgm^{-3}	*Concentration*	*Effects*
3 days	9400 18800 37600	slight interstitial oedema epithelial necrosis and interstitial inflammatory infiltration as for 10 ppm plus intra-alveolar oedema, thickening of pulmonary arteries
25 days	18800	emphysema, slight centrilobular interstitial fibrous, thickening of pulmonary arteries

Overall there is no evidence to suggest that exposure to normal outdoor concentrations of NO_2 is likely to give rise to emphysema. Concentrations in some indoor environments may approach those associated with initial changes in lung tissue that may precede emphysema.

4.9 EFFECTS ON DNA

Kikugawa et al (1994) demonstrated that exposure to NO_2 can induce damage to amino acids and proteins and a review by Victorin (1994) found some evidence that NO_2 is genotoxic *in vitro*. There was no clear evidence that NO_2 causes cancer although lung adenomas were induced in the susceptible strain A/J mouse. Metabolites of NO_2 include nitrate which is devoid of genotoxic properties and nitrite which has been shown to be genotoxic *in vitro*, although cancer studies have been mainly negative.

More recently the WHO (1997) concluded that NO_2 causes mutation in bacteria but not in mammalian cells *in vitro* or Drosophila or in mice *in vivo*. The WHO concluded that there is limited and conflicting evidence that NO_2 can promote or enhance the production and growth of tumours caused by other agents. Luhr et al (1998), however, report that NO_2 has been shown to induce chromosome aberrations in both animal and bacterial test systems.

Bermudez (1999, 2001) suggested that the toxic effects of NO_2 and O_3 are mediated through the formation of free radicals that can cause DNA strand breaks. No effects on the production of an enzymatic marker of DNA repair by alveolar macrophages were found following exposure to concentrations of 2 µgm^{-3} of NO_2 over three days. Walles et al (1995) previously found that exposure of mice to 56 400 µgm^{-3} of NO_2 for 16 hours or 94 000 µgm^{-3} for 5 hours gave rise to single strand breaks. Experiments with rats undertaken by Bittrich et al (1993) showed that NO_2-induced DNA single strand breaks in V79 cells are inhibited by anti-oxidative vitamins. The relevance of effects found at high levels of exposure to understanding the effects of ambient air pollution is unclear.

A number of authors have suggested that inhaled NO_2 may react with other substances to form carcinogens. Miyanishi et al (1996), for example, observed the *in vivo* formation of mutagens when polyaromatic hydrocarbons were injected into the peritoneum of rats, guinea pigs and hamsters. The results of experiments with diesel particulate suggest that NO_2 and/or SO_2 may promote lung tumour induction by DEP extracts (Ohyama et al, 1999).

4.10 REPRODUCTIVE EFFECTS

There is relatively little information about the effects of NO_2 on reproduction. Di Giovanni et al (1994) found evidence that exposure of pregnant rats to concentrations of NO_2 up to 5640 µgm^{-3} was associated with subtle behavioural changes in rat offspring, particularly with respect to the length and frequency of ultrasonic calls made by 10 day and 15 day old rats. The WHO (1997) concluded that exposure of rats to concentrations of NO_2 of up to 1800 µgm^{-3} for 7 hours/day, 5 days a week for 21 days had no effect on male fertility. The exposure of male and female rats to 2400 µgm^{-3} for 12 hours/day for 3 months was associated with reduced litter size and neonatal weight. The exposure of pregnant females to concentrations of

1000 μgm^{-3} throughout gestation caused maternal toxicity which in turn had adverse effects on prenatal development. Overall, it seems highly unlikely that exposure to ambient concentrations of NO_2 would adversely affect reproductive health.

4.11 EFFECTS ON CIRCULATION

Li et al (1994) found that exposure to NO_2 increases phosphatidylserine (nitrogen-containing phospholipid) content in the plasma membranes of pulmonary artery endothelial cells. Exposure of cells to 9400 μgm^{-3} NO_2 increased uptake and incorporation of exogenous l-serine into whole cells, total cellular lipids and phospholipids. Exposure to NO_2 also increased the activity of phosphatidylserine synthase in pulmonary artery endothelial cells. This implies that high levels of exposure to NO_2 may be associated with increased secretion of phospholipids in the walls of the pulmonary arteries.

Kikugawa et al (1995) investigated damage caused to low density lipoproteins by NO_2 and the uptake of damaged lipoproteins by mouse macrophages. They found that the lipid oxidation induced by the exposure increased the binding between lipoproteins and macrophages leading to the development of lipid-laden foam cells. They suggested that it was therefore possible that NO_2 may have a role in the formation of atherosclerotic lesions. Barth et al (1995) found that the medial thickness of pulmonary arteries increased significantly after 3 days exposure to 37400 μgm^{-3} of NO_2 or 25 days exposure to 18800 μgm^{-3}. Exposure to 9400 μgm^{-3}, however, led to a thinning of medial thickness.

Overall, the results of a limited number of animal experiments suggest that it is possible that exposure to NO_2 could have an adverse effect on cardiovascular health, but it is not clear that such effects could occur at ambient concentrations of NO_2.

4.12 EFFECTS ON WHOLE BODY HEALTH STATUS

In reviewing the extrapulmonary effects of NO_2, the WHO (1997) reported that extremely high levels of exposure were associated with methemoglobina. The no effects level in mice was 1500 μgm^{-3}. Januszkiewicz and Mayorga (1994) found effects in sheep following exposure to concentrations of 940 mgm^{-3} for 15 minutes. Their findings are unlikely to have relevance to understanding the effects of ambient NO_2.

Possible effects on liver function were reported in mice at concentrations of 470 μgm^{-3}. Possible effects on kidney function were found in guinea pigs exposed to concentrations of 940 μgm^{-3} for 14 days (proteinuria).

Umezu et al (1993) found that exposure to rats to 11280, 15040 and 22560 μgm^{-3} for 48 hours had a concentration-dependent effect on levels of eating and drinking giving rise to a concentration dependent reduction in weight. The no effects level was 7520 μgm^{-3}.

4.13 EFFECTS OF NITROGEN DIOXIDE IN MIXTURES

A number of investigators have examined the effects of combined exposures to NO_2 and ozone. MAAPE (1995) reported that most investigations of the combined effects of NO_2 and O_3, have found synergistic effects when exposure to both gases is simultaneous and additive effects where exposures are sequential. They speculated that the endpoint measured and the species investigated may have contributed to this apparent effect. Most of the relevant experiments investigated reversible cellular or biochemical changes in BAL fluid and were not informative as to potential long term effects. The WHO (1997) also reviewed a number of studies of the effects of NO_2 in mixtures. There was no interaction of NO_2 with ozone with respect to morphological endpoints (eg changes in epithelial cells). There was some evidence that NO_2 and ozone had synergistic effects on some, but not all, biochemical endpoints, for

example, consumption of antioxidant enzymes. There were interspecies differences in the extent of synergy. With respect to resistance to infection, short term exposure to NO_2 and ozone had additive effects whereas medium term exposure had synergistic effects.

A number of more recent experiments have investigated possible synergism between NO_2 and ozone. Experiments with rats undertaken by Bermudez (1999, 2001) found no effects on the production of a enzymatic marker of DNA repair by alveolar macrophages following exposure to 2256 μgm^{-3} NO_2 alone over three days. Exposure to the combination of 2256 μgm^{-3} NO_2 and 600 μgm^{-3} O_3, however, caused a 53% increase in enzyme activity whereas exposure to 600 μgm^{-3} of O_3 alone caused only a 25% increase in activity. This suggests that NO_2 can have important synergistic effects with O_3. Rajini et al (1993) exposed rats to mixtures of O_3 and NO_2 and measured effects on cellular proliferation as assessed using 5-bromo-2'deoxyuridine. Effects of the combination on larger airways was greater than the calculated sum of the responses to the two individual gases for concentrations of 400 μgm^{-3} of O_3 and 13536 μgm^{-3} NO_2. Effects on small airways at 1600 μgm^{-3} O_3 and 27072 μgm^{-3} NO_2 were similarly greater than the summed effect of the individual gases. O'Neill et al (1995) reviewed the combined effects of O_3 and NO_2 and found evidence of a complex interaction. Whereas ozone and NO_2 have been reported to have synergistic effects in rats, experiments with human cell lines have found less than additive effects. Ozone is particularly associated with damage to proteins whereas NO_2 is associated with the peroxidation of lipids, nitrates and aromatic amino acids.

In practice, the interaction between NO_2 and ozone is likely to be of limited importance as concentrations of these pollutants in UK air tend to be inversely correlated, both in time and space (see sections 3.3.3). It is unlikely that populations within the UK would be simultaneously exposed to highly elevated concentrations of ozone and NO_2.

Relatively few investigators have looked at the interaction between NO_2 and particles, despite its possible importance in ambient air and the potential for exposures to elevated levels of particles and NO_2 to coincide both in time and space (section 3.3.2). MAAPE (1995) reported that an investigation of combined exposure to NO_2 and a sulphuric acid aerosol found synergistic effects with respect to raised protein levels in BAL fluid and collagen synthesis. The WHO (1997) concluded that experiments with NO_2 and acid aerosols did not show synergistic effects on clearance but did show additive, possibly synergistic effects on macrophage function. Synergistic effects were also found for collagen synthesis and the protein content of BAL fluids (a marker of lung damage). Drumm et al (1999) demonstrated that the cytotoxicity of combined particle – NO_2 exposures in experiments with human alveolar macrophages was greater than for particles alone. The NO_2, however, increased effects by less than 10%. Hubbard et al (1994) found that exposure of mice to NO_2 immediately after exposure to particulate silica greatly enhanced the inflammatory response associated with silica. More recently, Oehme et al (1996) have claimed a synergy between NO_2, O_3 and ammonium sulphate with the effects of the mixture being 340% of the effects of individual agents. There is also limited evidence that the effects of NO_2 on cellular immune functions may be enhanced by particle exposure. Polzer et al (1994) demonstrated that NO_2 modifies the immune functions of bovine alveolar macrophages and that effects were additive with those of toxic dusts such as quartz.

There is some very limited information about the effects of long term exposure to NO_2 and nitric oxide in dogs (Hyde *et al*, 1978) that suggests that the adverse respiratory effects observed (emphysema) were attributable to the NO_2 rather than the nitric oxide (WHO, 1997).

Overall, it seems likely that exposure to NO_2 enhances oxidative damage associated with exposure to other pollutants including particles but there is little experimental information to support this hypothesis.

4.14 NITRIC OXIDE

Nitric oxide is generated by the body and plays an important role in the regulation of a wide range of diverse physiological processes (Weinberger et al, 2001). It is a gaseous free radical that is poorly reactive with most biomolecules but highly reactive with other free radicals (Halliwell et al, 1999). Its ability to scavenge peroxyl and other damaging radicals make it an important antioxidant, particularly in the cardiovascular system. The enzymes that generate nitric oxide are active in airway epithelial cells, macrophages, neutrophils, mast cells, automic neurons, smooth muscle cells, fibroblasts and endothelial cells (Gaston et al, 1994). Endogenous NO plays an important role in killing bacteria and parasites and also in anti-tumour reactions. It also regulates pulmonary vascular resistance and may be necessary for the normal oxygenation of blood. Both endogenous and exogenous NO_x react readily with oxygen superoxide, water, nucleotides, metalloproteins, thiols, amines and lipids to form products with biochemical actions ranging from bronchodilation and bacteriostasis (s-nitrosothials) to cytotoxicity and pulmonary capillary leak (peroxynitrate) as well as those with mutagenic potential (nitrosamines). About 80-90% of inhaled NO is absorbed from the airways. Absorption decreases at very high levels of exposure because of lower levels of ventilation.

The WHO (1997) briefly reviewed the toxic effects of NO. Much less information is available than for NO_2. The adverse effects of NO on the airways are only observed at relatively high levels of exposure. The studies reviewed by WHO (1997) found no effects on pulmonary function in guinea pigs exposed to 19600 μgm^{-3} of NO. Increased airway responsiveness was observed following exposure to 6130 μgm^{-3} for 30 minutes, twice a week for 7 weeks. Reversal of metacholine-induced bronchoconstriction was reported in guinea pigs exposed to 6130 μgm^{-3}.

The reaction of nitric oxide with inhaled oxygen to form nitrogen dioxide can cause pulmonary irritation. Nitric oxide also reacts with superoxide anion to form peroxynitrite, a cytotoxic oxidant that can interfere with surfactant functioning (Weinberger et al, 2001).

NO causes similar damage to airways epithelium as NO_2, but at much higher levels of exposure (WHO, 1997). Epithelial hyperplasia was reported in mice exposed to 12300 μgm^{-3} for 6.5 months. Slight emphysema like alterations of alveoli were seen in rats exposed to 2460 μgm^{-3} but no effects were seen in mice with lifetime exposure to 2950 μgm^{-3}.

Inhaled nitric oxide also causes effects outside of the lung including blocking platelet aggregation, causing methemoglobina and possibly vasodilation (Weinberger et al, 2001). It is, however, rapidly inactivated in blood through reaction with haemoglobin.

Overall, there is little evidence from animal experiments that typical levels of exposure to ambient outdoor concentrations of nitric oxide are likely to give rise to toxic effects. The Health and Safety Executive have, however, issued a Chemical Hazard Alert Notice that recommends that concentrations of nitric oxide in workplace air should not exceed 1 ppm. Concentrations of nitric oxide adjacent to some roadsides may approach this level. It seems likely that the presence of NO in NO_x could substantially modify the effects of NO_2, but this has not been widely investigated in toxicological experiments.

4.15 PEROXYACETYL NITRATE

Peroxyacetyl nitrate (PAN) has an acute toxicity similar to NO_2, less than for O_3 and greater than SO_2. Short term exposure of animals to high concentrations can cause severe lung lesions and damage to epithelium of upper respiratory tract (Vyskocil *et al*, 1998). The threshold for pulmonary effects in sensitive individuals is close to 1.19-1.49 mgm^{-3}. Present ambient concentrations of PAN are unlikely to affect pulmonary responses to ambient ozone. In humans, the lowest level reported to cause eye irritation is 0.64 mgm^{-3} over 2 hours. Concentrations of 0.99 and 4.95 mgm^{-3} were identified as a no observed effect level and a no observed adverse effect level, respectively, for pathological and histological changes in the respiratory system of rats exposed to PAN in subchronic experiments (Vyskocil *et al*, 1998).

4.16 NITRIC ACID

The WHO (1997) only found a few studies of the toxicological effects of nitric acid. In one, normal and "allergic" sheep were exposed to concentrations of nitric acid vapour of 4120 μgm^{-3} for 4 hours. They found a decrease in specific pulmonary flow resistance (ie an absence of bronchoconstriction) in both sets of animals. The allergic sheep showed increased airway reactivity to carbachol both immediately and 24 hours after exposure. In another study, rats were exposed for 4 hours to 1000 μgm^{-3} of nitric acid vapour or 4 hours/day for 4 days to 250 μgm^{-3}. There was a decrease in the stimulated or unstimulated respiratory burst activity of alveolar macrophages recovered in BAL fluids and an increase in elastase inhibitory capacity of BAL fluids. There is no information about effects at levels of exposure more similar to those likely to arise in ambient air.

4.17 NITRATES

There is very little information about the toxicity of the nitrate salts that may form in ambient air as a secondary product of NO_x emissions. The WHO cite one study in which rats and guinea pigs were exposed to 1000 μgm^{-3} of ammonium nitrate for 6 hours/day, 5 days/week for 4 weeks. No significant effects were found on lung structure.

4.18 CONCLUSIONS

The results of animal experiments suggest that exposure to NO_2 is associated with a wide range of adverse effects on respiratory health including oxidative damage to lung lining fluid and airways cells, impaired immune function, inflammation, fibrosis and emphysema. The results of a limited number of experiments have suggested that adverse effects on cellular lipid metabolism that could contribute to the development of atherosclerotic lesions may also result from exposure to NO_2. This provides limited evidence of a possible role for NO_2 in the development of cardiovascular illness.

The adverse effects of exposure to NO_2 have generally only been reported in experiments where animals have been exposed to concentrations that are much greater than ambient levels. Exposure to concentrations of NO_2 that are similar to ambient concentrations during high pollution events has, however, been found to cause oxidative damage to airways surfactant in animals. This in turn may adversely affect clearance, lung function and ability to resist infection. Effects on the ability to fight infection have been reported in animals exposed to concentrations of NO_2 that are only marginally higher than those that occur in ambient air during high pollution events. The concentrations of NO_2 required to cause a measurable inflammatory response appear to be much higher than those found in ambient air.

For several of the health endpoints investigated in toxicological studies, it appears that the effects of NO_2 are dependent on both concentration and duration of exposure, although

concentration appears to be the more important of these variables. Short term exposure to peak concentrations appears to have a greater effect than exposure to the same dose over a longer time period. The results of most studies appear to be consistent with the existence of a threshold concentration below which no adverse effects would be expected in healthy individuals. Animal experiments, however, only utilise a limited number of animals and are unlikely to be representative of the full range of susceptibility that may exist in the human population. Levels of antioxidant activity within lung lining fluid have an important influence of susceptibility to oxidant induced damage suggesting that is likely that some individuals with low levels of antioxidants in pulmonary lining fluid would be more susceptible to the adverse effects of NO_2 than others in the general population. It also suggests diet may play a role in governing susceptibility to the adverse effects of oxidant gases.

There is limited evidence from some animal experiments that the inflammatory response developed on first exposure to NO_2 (at concentrations that are much higher than ambient), may progressively resolve during prolonged exposure. Markers of oxidative damage increase during the initial weeks of exposure, but then stabilise. This might imply that changes in NO_2 concentrations (eg such as arise during high pollution events) may have a greater influence on respiratory health than long term exposure. Epithelial damage in response to exposure to NO_2 does, however, progressively worsen with increasing duration of exposure, although effects have only been found at concentrations that are much higher than in ambient air.

The toxicity of NO is much less than that of NO_2 and NO is unlikely to play an important role in any adverse health impact associated with exposure to ambient NO_x. There is no toxicological evidence that exposure to secondary nitrate particles present in ambient air is likely to lead to adverse effects.

There is very little experimental data relating to the interaction of NO_2 and particles. Both pollutants are associated with oxidative stress and it is possible that NO_2 may enhance particle effects by depleting lung lining fluid of antioxidants. Anthony Seaton, however, believes that any contribution of NO_2 to oxidative stress is extremely small in comparison to the effects of ultrafine particles (personal communication, 2003).

Overall, the results of toxicological investigations in animals suggest that it is plausible that oxidant damage to airways surfactant may play a role in the association between NO_2 and adverse respiratory health effects observed in epidemiological studies. The evidence linking NO_2 to adverse cardiovascular effects is very limited, but an association seems possible. There is no evidence that exposure to ambient concentrations of NO_2 is likely to lead to serious lung injury.

5. EXPERIMENTS WITH HUMAN VOLUNTEERS

5.1 INTRODUCTION

This chapter updates previous reviews of the experimental studies of the effects of human exposure to nitrogen dioxide. The main aim of this chapter was to assess whether the findings of these studies support the hypothesis that low level exposure to NO_2 in ambient air may give rise to adverse health effects. A large number of experiments were conducted with human volunteers during the 1980s to determine the effects of inhaled NO_2. These were reviewed by MAAPE (1993) who found that the results were highly inconsistent between studies. Some studies found evidence of effects on respiratory function, airways responsiveness and symptoms at relatively low levels of exposure whereas others found no effects at much higher levels of exposure. There was limited evidence to suggest that some asthmatics were more susceptible to the adverse effects of NO_2 than other individuals. A more recent review by WHO (1997) came to broadly similar conclusions. Further experiments conducted during the latter part of the 1990s have largely focussed on the role of NO_2 in potentiating airways response to other pollutants including bioaerosols. Other studies have examined the role of NO_2 in causing changes in the cellular systems that normally protect the respiratory system from infection. A few studies have investigated the role of NO_2 in causing oxidative damage to the cells lining the airways. This chapter describes the key findings of studies reviewed by WHO (1997), the results of more recently published studies with NO_2 and the findings of the limited number of studies that have been performed with nitrous and nitric acids and nitrate salts.

Previous reviewers have commented on the difficulties associated with the interpretation of volunteer studies (MAAPE, 1993). The volunteers selected for these experiments are relatively healthy, even if suffering from asthma or chronic obstructive pulmonary disease. They are not therefore representative of the more general population. In addition the study panels are relatively small and may not include a representative cross section of susceptibility to effects, particularly if only a few percent or less of the population are susceptible. There is a difficulty in extrapolating from short term experimental exposure to relatively high concentrations of NO_2 to long term environmental exposure to low concentrations of NO_2, or even 24 hours exposure to elevated concentrations of NO_2 during high pollution events.

5.2 RESPIRATORY TRACT DOSIMETRY

Nitrogen dioxide is absorbed through the lower respiratory tract but deposition is greatest in the centriacinar region (junction between the conducting and respiratory airways; WHO, 1997). In healthy humans 81-90% of inhaled NO_2 is absorbed during normal breathing increasing to 91-92% during maximal ventilation (WHO, 1997). The received dose is much greater during exercise because of the greater volume of air inhaled. Increased ventilation rates lead to greater penetration of inhaled NO_2 and an increased absorption of NO_2 in the lower rather than upper airways (WHO, 1997).

5.3 ODOUR THRESHOLD

Nitrogen dioxide has a stinging, suffocating odour. The odour threshold for NO_2 has been placed at levels between 100 μgm^{-3} and 410 μgm^{-3} by different authors (WHO, 2000). The WHO (1997) report that lowest concentration at which healthy volunteers have detected NO_2 during experimental exposures is 75 μgm^{-3}. The nose adapts to NO_2 so that no odour was perceived during an experimental study in which concentrations were increased from 1 to 51000 μgm^{-3} over a 15 minute period.

5.4 AIRWAYS RESISTANCE AND LUNG FUNCTION

Most studies show no effects at exposure concentrations of up to 14000 μgm^{-3} in healthy volunteers, although some have found effects at concentrations as low as 282 μgm^{-3} (Table 5.1, WHO, 1997). The WHO cites studies that show inconsistent results and some findings have not been reproducible in subsequent studies by the same laboratories. Bylin (1993) reviewed 40 studies involving healthy volunteers and concluded that there were clear effects on pulmonary function at concentrations of 9400 μgm^{-3} and equivocal evidence for effects at 4700 μgm^{-3}. A greater proportion of experiments with asthmatics have found effects at concentrations of less than 14 000 μgm^{-3} than those with healthy subjects (WHO, 1997). Bylin (1993) reviewed 25 studies of asthmatics and found that most showed no effects at concentrations of 200- 1200 μgm^{-3}. Small effects were seen in some studies, however, at concentrations of 560 μgm^{-3}. Overall, there is no clear evidence from the studies reviewed by the WHO (1997) that effects increase with concentration or duration of exposure or that superimposition of peak exposures on a background level of exposure greatly alters observed effects. There is also no clear evidence that exercise clearly increases effects in healthy volunteers. There is limited evidence that exercise may increase effects on lung function in asthmatic volunteers. There is insufficient information to determine dose-response functions for either asthmatic or normal volunteers.

Table 5.1: Summary of results of human volunteer experiments investigating effects of NO_2 on airways resistance and lung function reviewed by WHO (1997)

Conditions	***Airways Resistance***		***Lung function***	
	Healthy subjects	***Asthmatics***	***Healthy subjects***	***Asthmatics***
lowest concentration associated with effects	282 μgm^{-3} – some individuals; 1316-3760 μgm^{-3}	940 μgm^{-3}	1880 μgm^{-3} – possible changes in FVC	564 μgm^{-3} (with exercise)
duration of exposure	2 hours (lower concentration) 10 minutes	2 hours	2 hours on consecutive days	30 minutes
highest no effects concentration	7250 μgm^{-3}	7520 μgm^{-3}	3760 μgm^{-3}	940 μgm^{-3}
duration of exposure	75 minutes	75 minutes	120 minutes	75 minutes

Some studies of patients with chronic obstructive pulmonary disease have found effects on airways resistance at 940 μgm^{-3} and lung function at 564 μgm^{-3}, but no information is available about the presence or absence of effects at lower levels of exposure (WHO, 1997). Other studies have reported no effects associated with 1 hour exposures to 3720 μgm^{-3} (Bylin, 1993). Vagaggini et al (1996) found a mild decrease in FEV_1 in COPD patients exposed to 572 μgm^{-3} NO_2 for 2 hours. Similar effects were not seen in healthy or asthmatic volunteers. Although individuals with COPD may be expected to be more sensitive to NO_2 than healthy subjects, they may have limited capacity to respond to NO_2 (WHO, 1997).

There is limited evidence to suggest that the lungs of volunteers adjust to NO_2 exposure so that the lung function effects of NO_2 decline with multiple exposure. Blomberg et al (1999) exposed volunteers to 3760 μgm^{-3} of NO_2 for 4 days. Significant decrements in FEV_1 and FVC were found after the first exposure to NO_2 but these attenuated with repeated exposures.

5.5 AIRWAYS RESPONSIVENESS (INCLUDING RESPONSE TO ALLERGENS)

Airways responsiveness has been studied in both healthy and asthmatic volunteers (Table 5.2). A variety of challenges have been used to assess airways responsiveness so that the results of different studies are not always directly comparable. The results of individual studies have not always been self consistent. For example, WHO (2000) highlight a study by Avol et al (1988) that found that reactivity to cold air was increased by exposure to 500 μgm^{-3}

but not 1130 µgm^{-3}. The effect was not reproduced in a subsequent study (Avol et al, 1989). Bylin (1993) reviewed 7 studies in healthy subjects and found no evidence of effects at concentrations of less than 2000 µgm^{-3}. A meta-analysis by Folinsbee (1992) found a statistically significant effect at concentrations greater than 1880 µgm^{-3}. Effects were largely concentrated in studies in which subjects did not undertake exercise and most of the studies in which subjects exercised during exposure found no effect on airways responsiveness. The results of some of the studies reviewed by the WHO (1997) suggest that effects in both healthy and asthmatic subjects may be related to both concentration and duration of exposure, although the evidence is extremely limited.

Table 5.2: Summary of results of human volunteer experiments investigating effects of NO_2 on airways responsiveness reviewed by WHO (1997)

Conditions	***Healthy subjects***	***Asthmatics***
lowest concentration associated with effects and associated duration of exposure	9400 µgm^{-3} for 14 hours 14100 µgm^{-3} for 2 hours	210 µgm^{-3} for 60 minutes (some doubts about study reliability) 260 µgm^{-3} for 30 minutes
highest no effects concentration	5640 µgm^{-3}	5640 µgm^{-3}
duration of exposure	120 minutes/day for 3 days	60 minutes

Since the WHO (1997) review was undertaken, a number of other studies of the effects of NO_2 on the allergic response of asthmatics have been undertaken and the results of these studies are summarised in Table 5.3. In general, the results of these studies indicate that exposure to concentrations of NO_2 of more than 500 µgm^{-3} increases the asthmatic response to a range of allergens. There is limited evidence of possible effects at concentrations of only 300 µgm^{-3}. Effects are observed on both immediate and delayed responses to allergen exposure. A review by Davies et al (1998) concluded that exposure to O_3 and NO_2 with or without SO_2 can enhance the airway allergic response in susceptible individuals such as those with asthma and rhinitis. These pollutants influence the actions and interactions of a variety of cells and lead to the synthesis of pro-inflammatory mediators that modulate the activity and functions of inflammatory cells. An earlier review (Davies et al, 1997) concluded that exposure to NO_2 and other pollutants is associated with increased levels of eosinophil cationic protein in nasal secretions suggesting that pollutants may prime eosinophils for subsequent activation by allergen. *In vitro* studies suggest that airways epithelial cells play an important role. Nasal epithelial cells cultured from biopsies show that cells from atopic individuals release significantly greater quantities of pro-inflammatory cytokines than those of non-atopic individuals and that that cytokine release is greatest during the pollen season. In addition to the effects of NO_2 on allergic response, the bioavailability of grass pollen allergens may be affected by air pollutants and this may complicate future epidemiological investigations of effects. Behrendt et al (1997) showed that *in vitro* exposure of pollen to SO_2 reduced levels of allergen release, but similar effects were not found with NO_2.

Table 5.3: Summary of results of human volunteer experiments investigating effects of NO_2 on airways reactivity

Study	*Exposure*	*Effect*
Jenkins et al (1999) – atopic volunteers	6 hours to 380 μgm^{-3} NO_2 (with intermittent moderate exercise) and subsequently for 3 hours to 762 μgm^{-3} NO_2.	exposure to 380 μgm^{-3} NO_2 did not cause any increase in the airway response to inhaled allergen whereas exposure to 762 μgm^{-3} caused a significant decrease in the dose of allergen required to decrease FEV_1 by 20%; effects associated with concentration rather than cumulative exposure
Svartengren et al (2000) - asthmatic volunteers	concentrations of NO_2 exceeding 300 μgm^{-3} in road tunnels	significantly greater early reaction following subsequent exposure to allergens than following an exposure to lower pollution levels in a suburban area. There were also greater effects on lung function and more asthma symptoms during the late phase reaction to an allergen. Similar, but smaller effects were found with $PM_{2.5}$.
Strand et al (1998) - volunteers with mild asthma	500 μgm^{-3} NO_2	Asthmatic response was significantly increased after repeated exposure to NO_2 and allergen compared to air and allergen. Mean fall in FEV_1 after NO_2 exposure was –25% versus –0.1% for air immediately after exposure and 4-4% vs –1.9% 200 minutes later. There was a tendency towards increased night time symptoms after NO_2 plus allergen.
Strand et al (1997) - 18 asthmatics with pollen allergy	490 μgm^{-3} NO_2 for 30 minutes	Late stage asthmatic reaction enhanced; peak expiratory flow after allergen challenge was 6.6% lower than for air control; NO_2 caused a nonsignificant increase in the number of subjects who experienced a late phase asthmatic reaction. No effects on allergen-induced increases in responsiveness to histamine.
Tunnicliffe et al (1994)	762 μgm^{-3} NO_2 for 1 hour	significant increase in early and late asthmatic response to house dust mite as assessed from FEV_1 at 2 hours and later
Mukala et al (1996) asthmatic volunteers	1140 μgm^{-3} NO_2 for 1 hour	no clinically important effect on the airways of adults or children, possible slight increase in airways hyper responsiveness in children
Rusznak et al (1996), asthmatic subjects	762 μgm^{-3} NO_2 and 200 ppb SO_2	Significant reduced quantity of *D Pteronyssinus* required to produce a 20% drop in FEV_1. Effects greatest 24 hours after exposure and last for 48 hours.
Wang et al (1995)	762 μgm^{-3} NO_2 for 6 hours	increased eosinophil activation in the early phase response to nasal allergen provocation
Devalia et al (1994) asthmatic volunteers	762 μgm^{-3} NO_2 and/or 1590 μgm^{-3} SO_2	no decreases in FEV_1 or FVC associated with either agent alone but a significant reduction in the quantity of *D pteronyssinus* allergen required to produce a 20% drop in FEV_1 following exposure to the 2 gases in combination.

5.6 SYMPTOMS

There is relatively little information about symptoms arising in volunteer experiments (Table 5.4). There is limited evidence to suggest asthmatics may experience symptoms at lower concentrations than healthy subjects. There is also limited information to suggest that symptoms are generally associated with slightly higher levels of exposure than subtle effects on airways resistance, lung function and airways responsiveness in healthy volunteers.

Symptoms may occur at similar levels to those associated with more objective measures of change in asthmatics (WHO, 1997). Vagaginni et al (1996), however found that exposure to 572 μgm^{-3} NO_2 for 2 hours was associated with a small increase in symptoms in healthy subjects or patients with COPD but not in asthmatics.

Table 5.4: Summary of results of human volunteer experiments investigating effects of NO_2 on respiratory symptoms reviewed by WHO (1997)

Conditions	***Healthy subjects***	***Asthmatics***
lowest concentration associated with effects	7520 μgm^{-3} – mild increase in symptoms	226 μgm^{-3}
duration of exposure	120 minutes	60 minutes
highest no effects concentration	3760 μgm^{-3}	7520 μgm^{-3}
duration of exposure	120 minutes	75 minutes

5.7 HOST DEFENCE SYSTEM

WHO (1997) found much less information about the effects of NO_2 on the host defence system of humans than was available for respiratory function parameters. Table 5.5 summarises the key findings of studies reviewed by WHO (1997, 2001). In general adverse effects seem to be associated with higher levels of exposure than those associated with subtle effects on airways resistance and reactivity. This may, however, merely reflect a paucity of information.

Table 5.5: Summary of results of human volunteer experiments investigating effects of NO_2 on host defence system reviewed by WHO (1997)

	Effect	*Concentration* μgm^{-3}	*Duration*
Lowest concentration associated with effects	Slight increase in circulating lymphocytes	1128	120 minutes/day for 4 days
	increased bronchial PMN and decreased macrophage phagocytosis	3760	240 minutes
	increased mast cells and lymphocytes in bronchioalveolar lavage (BAL) fluids	4230	20 minutes
	increased lymphocytes in BAL fluids	7520	20 minutes
	Reduced numbers of lymphocytes and mast cells in BAL fluids, reduced phagocytic activity	7520	20 minutes, every other day for 12 days
	Viral infectivity – not statistically significant, study had limited power to detect effects	5640	120 minutes/day for 3 days
	Reduced activity of alpha-1-protease inhibitor (protein that protects lung from connective tissue damage)	5640-7520	
No effects level	Cell counts in BAL fluids	1128	180 minutes also 120 minutes on 4 out of 6 consecutive days
	Nasal/ tracheobronchial clearance	1993	60 minutes
	Reduced activity of alpha-1-protease inhibitor (protein that protects lung from connective tissue damage)	2820	
	Markers of inflammation eg albumin, fibronectin, hyaluronan, angiotensin-converting enzyme, 2-microglobulin, lactate dehydrogenase, total protein, leukotriene B4, prostaglandin E2, tumour necrosis factor	10340	120 minutes/day for 4 days

This is an area of active research and a number of other studies have been published that demonstrate that exposure to high concentrations of NO_2 gives rise to an inflammatory response in healthy volunteers (Table 5.6). In asthmatic volunteers, an inflammatory response has been observed at lower levels of exposure, but at concentrations that are higher than those associated with an enhanced response to allergens. Antioxidants such as glutathione (GSH), uric acid, ascorbate and a-tocopherol present in pulmonary lining fluid are thought to protect the airways from oxidant injury (Blomberg, 2000). The results of studies of antioxidant activity in human volunteers suggest that antioxidants in lung lining fluids act as sacrificial substrates scavenging oxidant pollutants from the airways and thereby preventing oxidation of macromolecules such as lipids, proteins and carbohydrates (Blomberg, 2000). This in turn limits the extent of cellular damage that is induced by NO_2.

Table 5.6: Experimental investigations of the effects of NO_2 on inflammatory response and the host defence system in human volunteers

Study	*Exposure to NO_2*	*Effect*
Sandstrom et al (1992a and b) – healthy volunteers	repeated exposure to 2858 and 7620 μgm^{-3} for 20 minutes, every other day over 12 days	reduction in the numbers of B cells and natural killer cells in lavage fluids and a changed CD4+/CD8+ cell ratio. There were no effects on lymphocyte or mass cell numbers.
Devlin et al (1999) – healthy volunteers	3810 μgm^{-3}	increased numbers of neutrophils and levels of inflammatory mediators (IL-6, IL-8, alpha antitrypsin and tissue plasminogen activator) in bronchiolavage but not bronchioalveolar lavage fluids; no change in lung function detected but the aerosol bolus recovery technique was used to demonstrate small obstructive changes
Blomberg et al (1999)	3810 μgm^{-3} for 4 days	bronchial wash and bronchiolavage showed evidence of decreased neutrophil numbers in the bronchial epithelium combined with neutrophilic inflammation consistent with migration and activation of neutrophils in the airways; no evidence of changes in antioxidant status.
Blomberg et al (1997)- healthy nonsmoking subjects	3810 μgm^{-3} for 4 hours	increased levels of neutrophils in bronchioaveolar lavage fluids at 6 hours after exposure; evidence of increased interleukin-8 secretion at 1.5 hours after exposure; absence of adhesion-molecule up regulation or cellular inflammation in mucosal biopsy specimens indicating that the major site of inflammation following exposure to NO_2 may be in the smaller airways and not in the alveoli. Decreased levels of total protein, albumin, immunoglobulin A and soluble ICAM in bronchial wash fluids.
Strand et al (1997) - asthmatics with pollen allergy	490 μgm^{-3} for 30 minutes	greatly enhanced reaction to pollen but no indications of an inflammatory response as assessed from numbers of eosinophils or levels of eosinophil cationic protein
Magnussen et al (1994) - subjects with mild bronchial asthma	Not given in English abstract	changes in protanoid and leukotriene mediators but no changes in differential cells numbers – not found in healthy volunteers
Vagaggini et al (1996) – asthmatics	572 μgm^{-3} for 2 hours	Levels of eosinophils in induced sputum following were greater for asthmatics than for healthy subjects or those with COPD. The effects of NO_2, however, were not significantly different from those of air.
Kelly et al (1996)	3810 μgm^{-3} for 4 hours	Rapid loss of ascorbate and uric acid with concentrations returning to baseline levels in bronchial wash fluids after 6 hours and in BAL fluids after 24 hours; increase in GSH in bronchial wash and returning to baseline levels after 25 hours.
Rasmussen et al (1993) - healthy nonsmoking adults	4382 μgm^{-3} for 5 hours	24 hours after exposure there was a 14% decrease in serum glutathione peroxidase activity. Indications of a decrease in alveolar permeability were found 11 hours after the start. No irritation of mucous membranes or decrements in lung function were associated with exposure to NO_2.
Avisser et al (2000) – healthy volunteers	1140 and 2858 μgm^{-3} NO_2 compared with 400 μgm^{-3} O_3	unlike the stronger oxidant O_3, NO_2 does not decrease the activity of the antioxidant glutathione peroxidase in epithelial lining fluid,

Overall, the lowest concentration at which a possible inflammatory response has been detected in healthy volunteers is 1128 μgm^{-3}. A definite inflammatory response in the airways has only been detected at concentrations of 3760 μgm^{-3} or more. It is possible that inflammatory changes may occur in the airways of asthmatics at lower concentrations. Changes in antioxidant activity have been detected at concentrations exceeding 4000 μgm^{-3}. Future investigations over a wider range of concentrations and using more sensitive endpoints may find evidence of a toxicological response at much lower levels of exposure.

5.8 GENOTOXIC EFFECTS

Yadev and Seth (1998) found evidence of genotoxicity of NO_x in investigations of the effects of NO_x on somatic human chromosomes obtained from the lymphocytes of 45 goldsmiths exposed to concentrations of 1770.5 μgm^{-3} NO_x and an equal number of controls exposed to 50 μgm^{-3} NO_x. Effects were found for the mitotic index, chromosome aberrations, sister chromatid exchanges and satellite associations.

5.9 COMBINED EXPOSURES

The WHO (1997) found no evidence that NO_2 increased the response to other pollutants in experiments with pollutant mixtures. There was evidence, however that pre-exposure to NO_2 enhanced ozone-induced changes in airways responsiveness in healthy exercising subjects during subsequent exposure to ozone. Hazucha et al (1994), for example, found that exposure of healthy women (nonsmokers) to 1140 μgm^{-3} NO_2 for 2 hours with intermittent exercise had no effect on FEV_1 but did significantly enhance O_3-induced spirometric changes on subsequent exposure to 600 μgm^{-3} O_3. Drechsler Parks (1995) found that a combined 2 hour exposure to 1140 μgm^{-3} NO_2 and 90 μgm^{-3} O_3 reduced exercise induced cardiac output. The effect was not associated with O_3 alone.

Rigas et al (1997) examined the longitudinal adsorption of inhaled ozone in volunteers exposed to 1430 μgm^{-3} NO_2. They concluded that NO_2 increased the capacity of the lower airways to absorb O_3 because more of the biochemical substrates that are normally oxidised by ozone were made available.

Peden (1997) concluded from a review of the available studies, that SO_2 and NO_2 alone do not seem to have a priming effect is asthmatics but a combination of these two gases results in a heightened sensitivity to subsequently inhaled allergen.

Overall there is very limited evidence to suggest that exposure NO_2 may enhance the respiratory response to other pollutants. Any effects arising from the interaction of ozone and NO_2 are likely to be relatively unimportant in the UK as elevated concentrations of these pollutants in ambient air are unlikely to coincide in time or space (section 3.3).

5.10 NITROUS ACID, NITRIC ACID, NITRITE AND NITRATE SALTS

WHO (1997) provide a review of the relatively small number of studies of the effects of secondary pollutants that may arise in urban air from reactions involving NO_x. The findings of these studies are summarised in Table 5.7. More recently Beckett et al (1995) found that exposure of asthmatics to concentrations of 1270 μgm^{-3} of nitrous acid for 3 hours caused a significant decrease in FVC and an increase in respiratory and mucous membrane symptoms. Ramussen et al (1995) found changes in tear fluid cytology following exposure to nitrous acid. Concentrations of 0, 200 and 1000 μgm^{-3} HNO_3 were associated with increases in the number squamous cells of 20, 67 and 80%. There was also increased eye redness. Exposure to 1000 μgm^{-3} was also associated with a 10% decline in airways conductance following exercise. No effects were found on bronchial reactivity or lung function.

Table 5.7: Summary of results of human volunteer experiments investigating effects of compounds related to NO_2 reviewed by WHO (1997)

Substance	*Concentration μgm^{-3}*	*Effects*
Nitrous acid	8-760	Eye inflammation – dose dependent effects, no information about respiratory effects
Nitric acid	129 200 500	Decrements in lung function in adolescent asthmatics increased phagocytic activity in alveolar macrophages and increased resistance to infection No effects on lung function, airways resistance or cell counts in bronchioalveolar lavage fluids in healthy volunteers
Ammonium nitrate	200 (MMAD 1.1 µm)	No effects in healthy or asthmatic volunteers
Sodium nitrate	10-1000 (MMAD 0.2 µm) 7000 (M MAD 0.46 µm) 7000 (MMAD 0.49 µm)	No effects in asthmatic or healthy volunteers No effects in asthmatic or healthy volunteers Increase in airways resistance in patients with influenza

In summary, adverse effects associated with exposure to nitrous or nitric acid or nitrate particles have only been reported at concentrations that are at least 100 times greater than those likely to arise in ambient or indoor air. The results of these experiments provide no evidence to suggest that adverse effects are likely at the concentrations that these species occur in ambient air.

5.11 CONCLUSIONS

Experiments in which human volunteers have been exposed to known amounts of NO_2 have demonstrated effects on lung function, airways responsiveness and symptoms. They have also found evidence of an inflammatory response as assessed from increased levels of inflammatory cells and mediators and evidence of changes in antioxidant activity in the airways. The results of individual studies are highly inconsistent and it is impossible to determine exposure response relationships.

Asthmatics are generally more susceptible to effects than healthy volunteers and exposure to NO_2 may play an important role in enhancing the asthmatic response to inhaled allergens. The lowest concentrations at which effects on airways responsiveness have been seen in asthmatic volunteers are in the range of 200-300 μgm^{-3}. The results of some studies have suggested that effects on lung function and increased symptoms may also occur at these concentrations in asthmatics. Other studies have shown no effects at much higher concentrations. Exercise does not appear to increase susceptibility to effects on airways responsiveness in asthmatics, but it may lead to an enhancement in loss of lung function. Experimental exposures to NO_2 involve a few individuals who are unlikely to be fully representative of all asthmatics and are also of short duration. It seems plausible, therefore, that longer term exposure to the peak ambient concentrations of NO_2 during high pollution events may have a small adverse effect on the respiratory health of susceptible individuals. Effects may include enhancement of the response to inhaled allergens as well as enhancement of the adverse effects associated with other air pollutants capable of causing oxidative damage to the epithelial lining fluid such as ozone.

Exposure to secondary nitrous acid, nitric acid and nitrate particles at the concentrations present in ambient air is unlikely to have a measurable impact on health.

6. EPIDEMIOGICAL STUDIES: SHORT TERM EFFECTS

6.1 INTRODUCTION

This chapter reviews epidemiological investigations of the effects of nitrogen dioxide associated with the day to day variability in ambient concentrations. Reported effects include changes in daily death rate, increased numbers of emergency hospital admissions and visits, increased use of primary health care facilities, increased respiratory symptoms and reduced lung function. Each health endpoint is reviewed in detail below and an overall assessment of the strength of evidence linking NO_2 to observed effects is given at the end of each section. Ambient concentrations of NO_2 in most of the reviewed studies were generally slightly higher than current concentrations in UK cities. Concentrations of NO_2 were strongly correlated with those of particles in some, but not all of the reviewed studies. It was expected that the effects of NO_2, if any, on health would be almost immediate, whereas those of particles might develop over a few days. Inhaled NO_2 would immediately react with lung lining fluid whereas particles might persist to cause effects over several days. The lag between pollutant concentrations and effects was therefore considered as part of the review. It was also expected, on the basis of the results of toxicological and human volunteer studies, that the effects of NO_2 would be confined to high pollution episodes and the variability of NO_2 concentrations would be more important than mean levels. Pollutant concentrations were not, however, reported in the epidemiological studies in a way that made it possible to investigate the peakedness of exposures. Percentile concentrations are reported in many studies, but in the absence of a convention as to which percentile concentrations should be reported, the extent to which different studies may be compared is limited. Additionally percentile concentrations are only partially informative about the pattern of variability of pollutant concentrations. Mean concentrations of NO_2 in UK cities are only moderately correlated with the number of high pollution events (section 3.3.2), so that the reported mean concentrations of NO_2 in epidemiological studies are not necessarily informative about the frequency and intensity of high pollution events.

The main aims of this chapter were to:

assess the strength of evidence linking short term exposure to NO_2 to a range of health endpoints;

determine whether NO_2 has an effect on health that is independent of that of particles or whether affects attributed to NO_2 could be entirely due to confounding exposures;

determine whether NO_2 has an important modifying effect on the health impacts of particles;

select suitable concentration-response functions for use in a quantification of the health impacts of NO_2 in the UK.

The reviewed studies may not be fully representative of all studies that have been undertaken and there may have been some publication bias with respect to the non publication of studies that failed to detect effects. The studies were also of very variable size so the number of studies showing or not showing effects only gives a very general sense of the relative strength of evidence linking NO_2 to health effects. A more formal meta-analysis of single pollutant models was not conducted because, although it would have provided an apparently more precise estimate of the potential impacts of NO_2, it would not have helped to address the main issue which was whether the effects attributed to NO_2 in epidemiological studies are caused by NO_2 or some pollutant that covaries with NO_2. In addition, for endpoints other than mortality, there can be doubt about the exact comparability of the health endpoint measured in

different studies. Some, but not all studies will have attempted to separate the effects of NO_2 from those of other pollutants and different studies have considered different groups of pollutants.

A discussion at the end of the chapter reviews the evidence for an association between short term changes in ambient concentrations of NO_2 and adverse health effects. The overall plausibility of the apparent relationship between NO_2 and health is discussed in Chapter 10. The discussion in this chapter includes consideration of the possibility that apparent relationships between NO_2 and health are actually due to some other unmeasured component of traffic pollution such as ultrafine particles. The discussion also reviews the epidemiological evidence for an interaction between NO_2 and particles and the power of epidemiological studies to detect effects, given the high proportion of smokers in the general population and other important influences on personal exposure concentrations of NO_2.

The relative risks shown in the tables in this chapter are for single pollutant models, unless otherwise stated.

6.2 ACUTE MORALITY

6.2.1 Overview

There have been a large number of studies of the relationship between air quality and daily mortality and a substantial proportion of these have shown that NO_2 may contribute to observed effects. The major difficulty in interpreting the results of these studies is that of separating effects that are attributable to NO_2 from those arising from other components of the air pollution mix.

6.2.2 Cause of death

Most of the reviewed studies of the relationship between NO_2 and “all cause” or “all nonaccidental” deaths show significant associations (Table 6.1). Only some of these studies also showed significant associations between mortality and particles. In contrast, less than half the reviewed studies showed significant associations between respiratory or cardiovascular mortality and NO_2 and many showed no relationship with NO_2 (Tables 6.2-6.3). The association between NO_2 and respiratory deaths is not obviously stronger than that between NO_2 and cardiovascular deaths. The numbers of respiratory or cardiovascular deaths would be smaller than for total mortality and this may have weakened the power of studies to detect effects. The number of studies that found significant associations between measures of particle concentrations and respiratory deaths was only slightly greater than for NO_2. The proportion of studies that found significant associations between particles and cardiovascular deaths was similar to that for NO_2.

Relatively few investigators have reported a more detailed breakdown of cause of death and it is difficult to draw any general conclusions from the results of these studies. Most of the few studies that have specifically considered cerebrovascular deaths, have found a significant association with NO_2. The few studies that have considered deaths from COPD or pneumonia have also consistently shown a significant association with NO_2.

Table 6.1: Acute mortality-all cause (CI: confidence interval; SE: standard error; TSP: total suspended particulate; BS: black smoke)

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI or SE)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
7 Spanish cities involved in the EMECAM project	all nonaccidental By city Barcelona Gijon Huelva Madrid Oviedo Seville Valencia	32.9-71.0 53.6 45.1 32.9 71.0 50.4 58.9 66.8				**0.67** (0.415-0.926) **0.60** (0.08-1.11) 0.53 (-0.80-1.90) 3.52 (-0.6-7.8) **0.54** (0.1-0.97) 2.1 (-0.3-4.7) **1.11** (0.04-2.2) 0.9 (-0.04-1.9)	no info for **PM_{10}** NO_2+PM_{10}: 2.775 sig	Saez et al (2002)
EMECAM study Seville Madrid Huelva 2 cities of Asturias	 all cause all cause all cause all cause					 **2** not significant **4.14** (0.47-7.96) significant	 not significant not significant **3.59** (0.7-7.22) winter not significant	Ocana-Riola et al (1999); Galan Labaca et al (1999); Daponte Codina et al (1999); Canada Martinez et al (1999)
Seol, Korea, Patients with congestive heart failure	all cause patients with congestive heart failure general population	60.4	68.7	35.5	63.6 1 hr	 **4.06** (0.46-7.99)* 2.34 (-0.18-5.0)** 0.29 (-0.07-0.68)	 1.75 (-0.5-4.25) 1.37 (-0.26-3.11) **0.33** (0.14-0.52)	Kwon et al (2001) * case cross over design ** general additive model
France Rouen Le Harve	 total total	 34.82 37.27	BS 18.65 16.32	 19.70 33.72	 60.57 46.85	 **1.36** (0-2.66) 0.62 (-0.92-2.16)	BS 0.4 (-1.3-2.0) 0.3 (-1.4-1.9)	Zeghnoun et al (2001)
Phoenix USA	all cause	57.1	46.5 T	8.2	114	**1.8** (0.5-3.2)	**1.2** (0-2.0) TSP	Mar et al (2000)
Melborne, Australia	all cause	22.1	19		254	**2.4** (1.2-10.04)	0.3 (-0.06-0.12)	Simpson et al (2000)
California	all cause	5.7-38	29.8-47.4		124-134	1.44 (0-2.4)	0.41 (-0.41-0.82)	Ostro et al (2000)
South Korea	all cause	45.7	71.2	47.7	30.8	**1.37** (0.003)	0.8 (se 10.4)	Hong et al (1999)
London	all cause	64.2 (24 hr) 95.8 (1 hr)	28.5	21.2	35 (8 hr) 45.2 (I hr)	**0.58** (0-1.22)	0.4 (-0.3-1.0)	Bremner et al (1999)
Mexico City	infant mortality	71.8	27.4 $PM_{2.5}$	14.8	88.2	**2.91** (0.52-5.29)	**6.9** (2.5-11.1) $PM_{2.5}$	Loomis et al (1999)

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI or SE)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Rome	total city centre warm season	99.2	84.2	16.2	25.9	**0.43** (0.1-0.67) **0.55** (0.14-0.95) **1.1** (0.48-1.71)	**0.38** (0.09-0.68) **0.66** (0.30-1.02) **0.96** (0.49-1.44)	Michelozzi et al (1998)
Sydney, Australia	all cause	24.8	18		48	**0.78** (0.01-1.56)	**0.95** (0.31-1.60)	Morgan et al (1998)
Sao Paulo, Brazil	interuterine mortality	157	65	18.9	67.5	**1.3**	no effect	Pereira et al (1998)
The Netherlands Major cities only Rest of country	all cause all cause all cause	32 46 28	34 35 33	10 16 8	47 36 51	**0.42** (0.12-0.74) **0.64** (0.44-0.82) **0.62** (0.46-0.8)	0.08 (-0.31-0.49) **0.22** (0.05-0.4) **0.18** (0.03-0.34)	Hoek et al (2000)
Brisbane, Australia	all season	27 24 hour 55 1 hour	27	25.4 1 hour	48.4 1 hour	24 hour none	*1 hour - 0.29 (0.6)*	inferred **1.8** (0.6-3.0)	Simpson et al (1997)
	winter	31.2 24 hour				1.07 (0.7)			
Meta-analysis	all cause mortality					**0.62** (0.46-0.78)	**0.63** (0.38-0.77)	Stieb et al (2002a)
15 European cities	all cause					10 ug increase 1 hr max **0.26** (0.18-0.36)		Touloumi et al (1997)
Amsterdam	all cause	46	39	9	43	**0.44** (0.01-0.88)	0.28 (-0.01-0.58)	Roemer and van Wijnen (2001)
Buffalo, NY	all cause	39	24.1	32.33	52.4	0.55 (0.33)	**2.32** (0.94)	Gwynn et al (2000)
Mexico City	all cause	72	27	14.8	88 (163 I hour)	0.60 (-0.26-1.45)	**1.36** (0.20-2.52) $PM_{2.5}$	Borja Aburto et al (1998)
California	all cause: daily mean 1 hour max	34.1 70.3	56.8 67.1		128.4	1.46 (0.93) **1.19** (0.504)	**0.9** (0.4)	Ostro et al (1999)
Hong Kong	warm season cool season	48.1 63.8	42.2 61.7	18.3 17.2	32.0 35.1	0.14 (-0.22-1.11) **1.18** (0.48-1.9)	1.1 (-2.2-4.4) 1.6 (-0.8-4.0)	Wong et al (2001a)
29 European cities	total	low high					**0.19** (0.0-0.41) **0.80** (0.16-0.93)	Katsouyanni et al (2001)
Greater London (all year)	all cause	68.6	13 BS	82.2	28	0.15 (-0.02-0.31)	**1.13** (0.55-1.72)	Anderson et al (1996)
Birmingham	all cause	70.9	23.3	19.08	48 8 hr		0.1 (-0.7-0.8)	EPAQS 2001

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI or SE)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Helsinki	all cause	38	28	10	18	no effect	0.14 (-2.22-2.55)	Ponka et al (1998)
8 Canadian cities	all nonaccidental	41.4	28	10	18	3.9 (3.0)	1.9 (2.8)	Burnett et al (2000)
20 US cities	all cause					no effect	**0.51** (0.20-1.16)	Samet et al (2000)
Lyon, France	all nonaccidental	70	38 PM_{13}	47	10	0.4 (-0.4-1.5)	0.2 (-0.6-1.0) PM_{13}	Zmirou et al (1996)
Koln, Germany	all cause	72	34 PM_7	44		0.18	**0.34**	Spix and Wichmann (1996)
Barcelona, Spain	all cause all cause 70+ years	88.4 1 hour	49.7 BS	46	55.2	0.34 (0.13-0.55) 0.42 (0.17-0.68)	0.70 (0.29-1.12) 0.63 (0.16-1.13)	Sunyer et al (1996)
Santiago, Chile		>50	>50	>30		0.37	0.96 - $PM_{2.5}$	Cifuentes et al (2000)
3 Swiss cities	all cause Zurich Basle Geneva all cause 65+ years Zurich Basle Geneva	 58 53.9 59.4	TSP 46.2 45.2 nm	 35.4 26.5 40.2	 26.9 23.9 nm	 0.48 (0.25) **2.4** (0.48) **1.07** (0.50) 0.57 (0.28) **2.18** (0.54) **1.71** (0.36)	TSP 0.39 (0.20) **1.41** (0.28) na 0.53 (0.22) **1.31** (0.31) na	Wietlisbach et al (1996)

**mean maximum hourly*

Table 6.2: Acute mortality-respiratory

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Hong Kong	all respiratory disease chronic obstructive disease pneumonia and influenza	54.4	51.53	16.68	33.93	**1.3** (0.4-2.2) **2.3** (0.6-4.1) **1.6** (0.2-3.0)	**0.8** (0.1-1.4) **1.7** (0.2-3.3) 0.7 (-0.1-1.5)	Wong et al (2002a)
7 Spanish cities involved in the EMECAM project	respiratory	32.9-71.0				1.822 (-8.74-5.191)	NO_2+PM_{10}: 6.33 not significant	Saez et al (2002)
	separately for each city	53.6 45.1 32.9 71.0 50.4 58.9 66.8				1.426 (-0.3-3.1) 4.668 (-0.6-10.2) 1.55 (-9.4-13.8) **1.75** (4.8-3.0) 5.344 (-1.9-13.1) 1.482 (-2.1-5.2) 2.26 (-0.9-5.5)		
EMECAM study –Madrid Huelva	respiratory respiratory					not significant not significant	not significant **14.12** (3.0-26.4) winter	Ocana-Riola et al (1999); Galan Labaca et al (1999); Daponte Codina et al (1999); Canada Martinez et al (1999)
France Rouen Le Harve	 respiratory respiratory	 34.82 37.27	BS 18.65 16.32	 19.70 33.72	 60.57 46.85	 1.0 (-3.38-5.76) 3.87 (-0.94-9.18)	BS 2.0 (-3.9-8.6) 2.5 (-3.2-8.6)	Zeghnoun et al (2001)
Hong Kong	warm cool	48.1 63.8	42.2 61.7	18.3 17.2	32.0 35.1	1.1 (-0.22-2.86) **1.9** (0.48-2.86)	1.05 (-0.42-2.52) **0.97** (0-2.11)	Wong et al (2001)
Buffalo, NY	respiratory	39	24.1	32.33	52.4	1.64 (1.18)	3.29 (3.32)	Gwynn et al (2000)
Melborne, Australia	respiratory – all age respiratory – 65+ years	22.1	19		254	**4.5** (0.3-8.7) **4.9** (0.5-9.3)	none none	Simpson et al (2000)
California	respiratory	5.7-38	29.8-47.4		124-134	0.48 (-2.88-3.84)	none	Ostro et al (2000)
3 US counties Cook Los Angeles Maricopa	 COPD COPD COPD	 47.6 72.4 36.2	 35 44 41	 15.9 5.3 5.3	 36 48 50	 **1.18** (0.01-2.35) **0.98** (0.44-1.51) **2.36** (0.05-4.67)	 **1.06** (0.05-2.08) 1.16 (-0.04-2.68) 1.62 (-1.02-4.25)	Moolgavkar (2000)
South Korea	respiratory	45.7	71.2	47.7	30.8	0.84 (0.95)	2.7 (1.7)	Hong et al (1999)
California	respiratory	34.1 70.3	56.8 67.1		128.4	none	2.6	Ostro et al (1999)
London	respiratory	64.2 (24 hr)	28.5	21.2	35 (8 hr)	1.22 (-0.22-2.64)	**1.8** (0.4-3.4)	Bremner et al (1999)

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Sydney, Australia	respiratory	24.8	18		48	0.68 (-0.24-1.64)	**0.97** (0.09-1.87)	Morgan et al (1998)
Mexico City	respiratory >65 years	72	27	14.8	88 (163 I hour)	1.22 (-1.53-3.96) 0.39 (-0.76-1.54)	2.50 (-1.12-6.11)$PM_{2.5}$ **1.58** (0.04-3.12) $PM_{2.5}$	Borja Aburto et al (1998)
The Netherlands	COPD pneumonia	32	34	10	47	**1.8** (1.04-2.58) **2.92** (1.88-4.02)	**0.96** (0.14-1.85) **1.67** (0.58-2.87)	Hoek et al (2000)
Brisbane, Australia	respiratory	27 24 hour 55 1 hour	27	25.4 1 hour	48.4 1 hour	none / *1.0 (1.9)*	0.2 (-4.2-4.6)	Simpson et al (1997)
	winter respiratory	31.2 24 hour				1.49 (2.3)		
Sao Paulo, Brazil, children	respiratory disease							Saldiva et al (1994)
Greater London (all year)	respiratory	68.6	13 BS	82.2	28	none	0.44 (-1.08-1.99)	Anderson et al (1996)
Birmingham	respiratory	70.9 1 hour	23.3	19.08	48 8 hr		none	EPAQS 2001
Lyon, France	respiratory	70	38 PM_{13}	47	10	none	0.8 (0.0-1.8) PM_{13}	Zmirou et al (1996)
Paris, France	respiratory	45.0	31.9 BS	29.7	27.7 8 hour	0.57 (-0.78-2.13)	0.71 (-0.25-1.77) BS	Dab et al (1996)
Barcelona, Spain	respiratory	88.4 1 hour	49.7 BS	46	55.2	0.26 (-0.34-0.89)	0.97 (-0.10-2.15)	Sunyer et al (1996)
3 Swiss cities	respiratory Zurich Basle Geneva	 58 53.9 59.4	TSP 46.2 45.2 nm	 35.4 26.5 40.2	 26.9 23.9 nm	 2.03 (0.60) 3.46 (1.00) 2.41 (0.76)	TSP 1.38 (0.47) 0.99 (0.58) na	Wietlisbach et al (1996)

**mean maximum hourly*

Table 6.3: Acute mortality-circulatory

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Hong Kong	cardiovascular ischaemic heart disease cerebrovascular	54.4	51.53	16.68	33.93	0.8 (-0.1-1.6) **2.4** (1.2-3.6) none	0.3 (-0.2-0.8) **0.69** (0.60-0.83) 0.7 (-0.2-1.6)	Wong et al (2002)
Seol, Korea (NO_2 and PM_{10} poorly correlated)	stroke PM_{10} < 71.1 PM_{10} >71.1 NO_2<61.9 NO_2>60.9	61.9	71.1	32.1	45.2	**1.96** (0.7-3.22) 0.56 0.64	**0.69** (0.60-0.83) 4.8 -1.5	Hong et al (2002)
7 Spanish cities involved in the EMECAM project	cardiovascular separately for each city	32.9-71.0 53.6 45.1 32.9 71.0 50.4 58.9 66.8				1.127 (-0.06-23.14) **1.026** (0.10-1.96) 1.763 (-0.55-4.31) 2.036 (-0.45-9.07) **0.91** (1.96-1.63) 3.366 (-0.99-7.91) **2.429** (0.82-4.06) 0.617 (-0.88-2.14)	no info for PM_{10} NO_2+PM_{10}: 6.49 sig	Saez et al (2002)
Seville Madrid Huelva	cardiovascular cardiovascular cardiovascular					3 significant no association	not significant significant no association	EMECAM study
France Rouen Le Harve	 cardiovascular cardiovascular	 34.82 37.27	BS 18.65 16.32	 19.70 33.72	 60.57 46.85	 **3.6** (0.88-6.44) 1.8 (-0.92-4.7)	BS 2.8 (-0.3-6.0) 1.7 (-1.4-4.9)	Zeghnoun et al (2001)
Hong Kong	Cardiovascular-warm cardiovascular-cold	48.1 63.8	42.2 61.7	18.3 17.2	32.0 35.1	none 0.24 (-0.72-1.42)	none 3.2 (-0.8-7.3)	Wong et al (2001)
Phoenix USA	cardiovascular	57.1	46.5 T	8.2	114	**3.2** (1.3-5.0)	**2.0** (0.4-3.6) TSP	Mar et al (2000)
Buffalo, NY	cardiovascular	39	24.1	32.33	52.4	0.33 (0.56)	3.28 (1.60)	Gwynn et al (2000)
California	cardiovascular	5.7-38	29.8-47.4		124-134	0.96 (-0.48-2.4)	**1.22** (0.41-2.03)	Ostro et al (2000)
3 US counties Cook Los Angeles Maricopa	 cardiovascular cerebevascular cardiovascular cerebevascular cardiovascular cerebevascular	 47.6 72.4 36.2	 35 44 41	 15.9 5.3 5.3	 36 48 50	 **0.54** (0.12-0.97) 0.62 (-0.15-1.40) **0.73** (0.54-0.92) **0.70** (0.34-1.06) **1.21** (0.12-2.29) **2.08** (0.17-4.00)	 **0.44** (0.07-0.81) 0.65 (-0.03-1.33) **0.88** (0.32-1.44) 0.58 (-0.47-1.63) **1.73** (0.51-2.95) **2.12** (0.02-4.22)	Moolgavkar (2000)

Location/ population	*Cause of death*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
South Korea	cardiovascular	45.7	71.2	47.7	30.8	2.31 (2.21)	**1.0** (se 0.5)	Hong et al (1999)
California	cardiovascular	34.1 70.3	56.8 67.1		128.4	none	**1.6**	Ostro et al (1999)
London	cardiovascular	64.2 (24 hr) 95.8 (1 hr)	28.5	21.2	35 (8 hr) 45.2 (I hr)	**1.22** (0.38-2.06)	0.8 (-0.1-1.7)	Bremner et al (1999)
Helsinki	cardiovascular	38	28	10	18	no effect	1.27 (-2.47-5.14)	Ponka et al (1998)
Sydney, Australia	cardiovascular	24.8	18		48	2.25 (-0.10-4.78)	1.21 (-0.77-3.3)	Morgan et al (1998a)
Mexico City	cardiovascular	72	27	14.8	88 (163 I hour)	0.74 (-0.87-2.35)	2.19 (-0.01-4.38)$PM_{2.5}$	Borja Aburto et al (1998)
The Netherlands	cardiovascular disease	32	34	10	47	**0.56** (0.3-0.82)	0.015 (-0.013-0.43)	Hoek et al (2000)
the Netherlands	all cardiovascular MI and other IHD Arrhythmia Heart failure Cerebrovascular Embolism, Thrombosis					**0.77** (0.3-0.12) 0.57 (-0.07-1.17) 1.00 (-0.8-2.93) **2.1** (0.8-3.12) **1.6** (0.6-3.39) 0.07 (-2.8-2.07)	0.15 (-0.2-0.52) 0.06 (-0.45-0.6) 0.52 (-0.85-2.04) 0.45 (-0.5-1.23) 0.39 (-0.29-1.17) 1.25 (-1.57-1.78)	Hoek et al (2001)
Brisbane, Australia	all season cardiovascular	27 24 hour	27	25.4 1 hour	48.4 1 hour	24 hour none	*1 hour - check* *none*	inferred none (-0.4-0.4)	Simpson et al (1997)
	winter cardiovascular	31.2 24 hour				1.55 (1.2)			
Greater London (all year)	cardiovascular	68.6	13 BS	82.2	28	0.12 (-0.11-0.36)	0.41 (-0.39-1.23)	Anderson et al (1996)
Birmingham	cardiovascular	70.9 1 hour	23.3	19.08	48 8 hr		0.4 (-0.7-1.5)	EPAQS 2001
Lyon, France	cardiovascular	70	38 PM_{13}	47	10	0.2 (-0.8-1.0)	0.8 (-0.2-2.0) PM_{13}	Zmirou et al (1996)
Barcelona, Spain	cardiovascular	88.4 1 hour	49.7 BS	46	55.2	**0.38** (0.09-0.68)	**0.93** (0.36-1.53)	Sunyer et al (1996)
3 Swiss cities	cardiovascular Zurich Basle Geneva	 58 53.9 59.4	TSP 46.2 45.2 nm	 35.4 26.5 40.2	 26.9 23.9 nm	 0.30 (0.37) 2.59 (0.75) 1.07 (0.50)	TSP 0.28 (0.29) 1.70 (0.43) na	Wietlisbach et al (1996)

**mean maximum hourly*

6.2.3 Size of effect

The estimated increment in daily death rate associated with an increase of 10 μgm^{-3} NO_2 is very variable. The original studies report effects for very different ranges of NO_2 and some errors are likely to have occurred in scaling effects to a common scale. The statistical methods used by different groups may have also contributed to the variability in reported concentration-response relationships. Kwon et al (2001), for example, show how the use of a different statistical model can give rise to an almost two-fold difference in the apparent size of the increment in mortality associated with NO_2. The findings of most studies tabulated in Tables 6.1 to 6.3 suggest that an increment in concentrations of NO_2 of 10 μgm^{-3} is associated with a less than 1.5% increase in daily mortality rate (all, cardiovascular or respiratory deaths). The results of a substantial proportion of these studies suggest that an increment of 10 μgm^{-3} in concentration would be associated with an increase of about 0.5% in the daily death rate. There is no relationship between the size of the reported effect of NO_2 on mortality in different studies and mean concentrations of NO_2 or PM_{10} (Fig. 6.1).

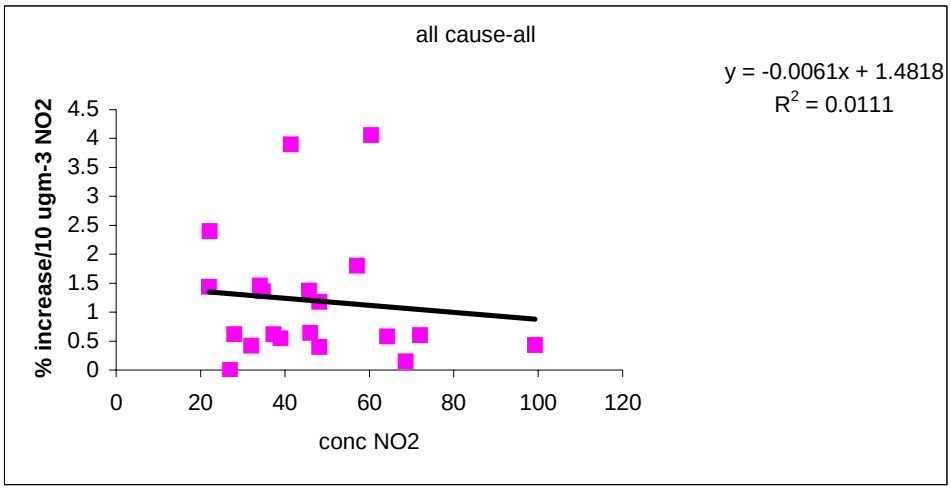

Figure 6.1: Relationship between estimated impact of NO_2 on acute mortality and mean concentrations of NO_2 in studies listed in Tables 6.1-6.3

6.2.4 Lag with respect to daily concentrations

Most studies have investigated the strength of association at different time intervals following peak pollutant concentrations. Cifuentes et al (2001), for example, demonstrated that significant associations between NO_2 or PM_{10} and mortality only existed where the deaths followed rather than anticipated high pollution episodes. Some studies have shown that associations for PM_{10} are strongest on the same day or following day whereas associations for NO_2 are strongest 2 or 3 days later (eg Michelozzi et al, 1998; Gwynn et al 2000) whereas other have found the reverse (eg Ostro et al, 1999). In others the lag for both pollutants is similar eg 3 days for acute mortality in London (Bremner et al, 1999). In general the difference in the strength of association for lags of 1 to 5 days or for averages over different numbers of days up to a week, is very small. There is no overall pattern of association that suggests that effects are more strongly associated with the same day concentrations of NO_2 than concentrations several days immediately previous to death (Table 6.4).

Table 6.4: Lag between pollutant concentrations and effects

Study	*Cause of death*	*NO_2*	*PM_{10}*
Wong et al (2002)	All	0-1	1
	COPD	0-2	0-3
	Pneumonia and influenza	0-3	2
	cardiovascular	0-2	2
	ischaemic heart disease	1	0-3
	cerebrovascular	1	2
Hong et al (2002)	stroke	2	
Zeghnoun et al (2001)	Rouen		BS
	total	0-3	1
	cardiovascular	0-1	1
	respiratory	1	0-1
	Le Harve		
	total	1	0-1
	cardiovascular	1	0-3
	respiratory	0-1	0-1
Wong et al (2001)	all nonaccidental, cardiovascular, respiratory	1-2	1-2
Simpson et al (2000)	respiratory	0	0
Mar et al (2000)	all	1	0
	cardiovascular	4	0
Gwynn et al (2000)	all cause	3	2
	cardiovascular	2	2
	respiratory	1	0
Moolgavkar (2000)	Cook		
	cardiovascular	3	3
	respiratory	1	1
	cerebrovascular	1	1
	Los Angeles		
	cardiovascular	1	2
	respiratory	1	1
	cerebrovascular	2	3
	Maricopa		
	cardiovascular	2	1
	respiratory	3	1
	cerebrovascular	2	5
Hoek et al (2000)	all cause	0-6	0-6
Campbell and Tobias (2000)*	all cause	2	3 (BS)
Cifuentes et al (2000)	all cause	2	**2**
Hong et al (1999)	all cause	1	0-4
	respiratory	0-4	0-4
	cardiovascular	1	0-4
Loomis et al (1999)	infant mortality	3-5	3-5 ($PM_{2.5}$)
Ostro et al (1999)	all cause	0	2
Bremner et al (1999)	all cause	1	1
	cardiovascular	3	3
	respiratory	1	1
Michelozzi et al (1999)	total	2	0
Borja Aburto et al (1998)	total, cardiovascular, respiratory	0-4	0 or 4 ($PM_{2.5}$)
Simpson et al (1997)	all cause, cardiovascular, respiratory	0	0
Dab et al (1996)	respiratory	1	1 BS
Sunyer et al (1996)	all cause, cardiovascular	1	1
	respiratory	0	3
Zmirou et al (1996)	all nonaccidental	1	0 PM_{13}
	respiratory	2	0
	cardiovascular	1	2
Wietlisbach et al (1996)	all cause, cardiovascular, respiratory	3	3
Anderson et al (1995)	all cause	1	1
	cardiovascular	0	1

**concentration-response relationships not reported in a format compatible with tables 6.1-3*

6.2.5 Vulnerable populations

The results of a number of studies suggest that older people may be more susceptible to the effects of air pollution than adults of working age. For example, Bremner et al (1999) reported that the effect of PM_{10} on the risks of death from respiratory causes was greater for people aged 65+ years. Katsouyanni et al (2001) found that the increase in daily death rate associated with PM_{10} was slightly higher for the elderly than for all ages. Simpson et al (2000) found that the effects of both NO_2 and particles on daily mortality from respiratory causes were marginally greater for those aged 65+ years than for the general population (difference not significant). Sunyer et al (1996) found that the increased risk of daily mortality associated in NO_2 was marginally higher for those over 69 years in age than for all ages. Zmirou et al (1996) report that the average age of people who die on high pollution days is slightly greater than that for other days. Although several authors have specifically considered infants and children, these studies have not looked at simultaneous effects on the adult death rate, so a comparison of strength of effect is not possible.

There is limited information to suggest that people with pre-existing illnesses may also be more susceptible to the effects of air pollution. Kwon et al (2001) found that the effects of NO_2 and PM_{10} on daily mortality were much higher for patients with congestive heart failure than for the general population. For these patients, the effects of NO_2 were also greater for a subgroup that had been admitted to hospital during the 4 weeks preceeding death and also for older patients.

Campbell and Tobias (2000) found that the increase in deaths found on days with elevated levels of NO_2, particle and ozone was followed by a reduction in daily death rate 5 or 6 days later. They suggested that this was consistent with at least some of the extra deaths only having been brought forward by a few days.

Hoek et al (2000) showed that the effects of NO_2 and PM_{10} on daily mortality were marginally (not significantly) higher in areas of the Netherlands outside of the major cities than in the major cities. Both the rural population and rural air pollution are likely to be different from those in urban areas.

Roemer and van Wijnen (2001) showed that the effects of background concentrations of NO_2 and PM_{10} on daily mortality were greater for those living beside main roads than for the general population. They attributed this to the higher levels of exposure to traffic pollutants among those living alongside main roads as the study had not specifically allowed for the potentially higher exposure of this subpopulation. The apparent effects of NO_2 and PM_{10} appeared to be over-estimated, if background concentrations were used as a proxy for exposure for the whole population. The levels of exposure of those living beside main roads was probably lower, however, than the measured roadside concentrations.

Overall, the limited information available is consistent with an increased susceptibility to the effects of air pollution in the elderly. The results of the reviewed studies of daily mortality do not suggest that specific vulnerability to nitrogen dioxide exists.

6.2.6 Seasonal effects

Time of year and climatic factors have important modifying effects on the relationship between air quality and acute mortality. Seasonal differences would include differences in pollutant mix as well as temperature and humidity. Wong et al (2001) found that air pollution had stronger effects on daily mortality in the cool season than in the warm season. Wong et al (2000), however, show a somewhat bigger seasonal effect in Hong Kong than in London despite a smaller seasonal variation in temperature. Similarly Simpson et al (1997) found that the effects of NO_2 on mortality in Brisbane greater during the winter than during the summer.

Concentrations of oxidant pollutants appeared to be a better predictor of effects than particles. Simpson et al (2000), however, reported that the effects of NO_2 and PM_{10} on respiratory mortality in Melborne were greater in the warm season. Michelozzi et al (1998), Anderson et al (1995), Sunyer et al (1996) and Hoek et al (2000) also found greater effects during the warm season. Cifuentes et al (2000) found season had little influence on the effects of NO_2 or particles on mortality. Overall there appears to be no consistent interaction between time of year and NO_2. Extremes of temperature, either hot or cold, are likely to be associated with an increased risk of mortality. The seasonal variation in pollution mix is likely to vary substantially between different parts of the world, particularly with respect to the generation of secondary pollutants by photochemical activity. It may be difficult to separate effects due entirely to temperature from those due to the interaction between temperature and air quality.

6.2.7 Evidence for an independent effect of NO_2

A large number of studies have found an association between air quality and daily mortality but the importance of any individual pollutant in the overall mix is unclear. There is a growing consensus that daily mortality is most strongly associated with particles and that fine particles arising from combustion are the most important component of particle pollution (EPAQS, 2001). Generally the results of recent studies of the relationship between air quality and mortality suggest that NO_2 has little or no effect on daily mortality (eg Sunyer and Basagana, 2001). Many recent studies have only investigated mortality in relation to various indices of particle pollution and have not considered gaseous pollutants in detail. The results of other studies, however, strongly suggest that NO_2 does play a role in the relationship between air quality and daily mortality. Moolgavkar (2000), for example, found that gaseous pollutants were more strongly associated with mortality than particles.

In most studies, the main problem in determining whether NO_2 has an independent effect is that in individual studies, concentrations of NO_2 are generally strongly correlated with those of particles. Concentrations of NO_2 and PM_{10} or black smoke were strongly correlated, for example, in the studies by Wong et al (2002), Simpson et al (2000), Hoek et al (2000), Kwon et al (2001), Borja Aburto et al (1998), Anderson et al (1995) and (Zeghnoun et al, 2001). Although, significant associations between mortality and NO_2 were not found in all of these studies, PM_{10} was similarly not consistently associated with daily mortality. In many of the listed studies in which PM_{10} and NO_2 were less strongly correlated ($r<0.6$), significant relationships between mortality and NO_2 were not found (see Hong et al, 2002; Gwynn et al, 2000; Moolgavkar, 2000; Simpson et al, 1997). There are also, however, a number of reports of significant associations between mortality and NO_2 in studies where NO_2 and PM_{10} were not strongly correlated (Table 6.5). In the study by Ostro et al (2000), concentrations of PM_{10} were heavily influenced by mineral dust as opposed to vehicle emissions so that concentrations of NO_2 and PM_{10} were extremely poorly correlated. There is no significant difference in the size of the apparent effect of NO_2 on mortality in studies where NO_2 and particles were strongly correlated and that found in studies where NO_2 and PM_{10} were less strongly correlated. Mean concentrations of NO_2 and particles across studies are only weakly correlated suggesting that it may be possible to undertake a cross study comparison that would have greater power to detect the effects of NO_2 than an individual study (Fig. 6.2).

Table 6.5: Examples of studies that have reported an association between NO_2 and acute mortality in the absence of a strong correlation of concentrations of NO_2 and particles

Cause of death	*Examples of studies where significant relationships with NO_2 found*
all cause	Phoenix, USA – Mar et al (2000); California – Ostro et al (2000); Barcelona – Sunyer et al (1996)
cardiovascular	Phoenix, USA – Mar et al (2000); Barcelona – Sunyer et al (1996)
cerebrovascular	Korea – Hong et al (2000)
respiratory	3 US Counties – Moolgavkar (2000)

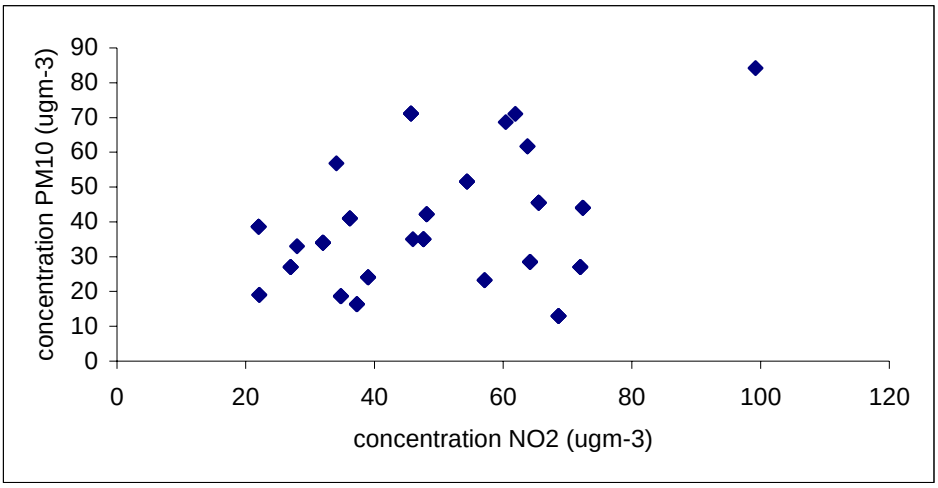

Figure 6.2: Relationship between mean concentrations of NO_2 and PM_{10} in the reviewed studies.

A large number of studies have compared the findings of single pollutant and multi-pollutant models. Most of these studies have shown that the apparent effects of NO_2 are much reduced in multipollutant models whereas those of particles are generally little changed. A few studies have shown reductions in the apparent effects of both NO_2 and particles and some have shown a reduction in the apparent effect of particles but little effect on that of NO_2 (Table 6.6). Differences in statistical methods may account for some differences between studies.

Table 6.6: Comparison of apparent effects of NO_2 in single and multi pollutant models.

Study	*Cause of death*	*Change in apparent effect of NO_2 or particles in multipollutant compared with single pollutant models*
Loomis et al (1999)	infant mortality	reduction in effect of NO_2 and little change in effects of $PM_{2.5}$ in 2 pollutant model. In 3 pollutant model with ozone, the percent change associated with 10 ppb NO_2 was 0.44 compared with 5.54 for single pollutant model. The percent change for 10 μgm^{-3} $PM_{2.5}$ was 6.4 compared with 6.87 in the one pollutant model.
Morgan et al (1998)	all cause cardiovascular	effect of NO_2 much reduced in multipollutant models
Morgan et al (1998)	respiratory	little change in effect of NO_2, effect of particles greatly reduced
Hoek et al (2000)	all cause, cardiovascular, respiratory	effects of PM_{10} reduced in two pollutant models with NO_2, effects of NO_2 slightly increased
Cifuentes et al (2000)		effects of both NO_2 and $PM_{2.5}$ slightly reduced in two pollutant models; effects of PM_{10} reduced in two pollutant models with various measures of fine particles; effects of NO_2 not greatly changed by inclusion of fine particles.
Kwon et al (2001)	all cause	Effects of PM_{10} disappeared in 2 pollutant model with NO_2 whereas that of NO_2 slightly increased
Samet et al (2000)	all cause	inclusion of NO_2 slightly reduces apparent effect of PM_{10}, but influence of NO_2 much smaller than that of ozone
Wong et al (2001)	cardiovascular, respiratory	addition of NO_2 to multipollutant models has little influence on the apparent effect of particles
Burnett et al (2000)	all accidental	effects of NO_2 greatly reduced in 2 pollutant models
Touloumi et al (1997)	all cause	effects of NO_2 halved in multipollutant models
Gwynn et al (2000)	all cause, cardiovascular, respiratory	effects of PM_{10} increased in two pollutant model with NO_2
Wietlisbach et al (1996)	all cause, cardiovascular, respiratory	effects of NO_2 and TSP ceased to be significant in multipollutant models

Although the main difficulty in the identification of an independent effect with NO_2 is confounding by particle pollution, other pollutants may also obscure the relationship between NO_2 and mortality. Simpson et al (2000), for example, were unable to separate the effects of particles from those of NO_2 and O_3.

Overall the results of the studies of acute mortality reviewed here are generally consistent with the existence of an association between mortality and NO_2 that is independent of the relationship between mortality and particles measured as PM_{10} or black smoke. The results of the tabulated studies do not, however, give a fair indication of the ratio of studies where significant effects have been found to be associated with NO_2 versus those where effects were not found. Publication bias is likely to have reduced the proportion of published studies that report no effects. In addition, the literature search specifically identified studies that had nitrogen dioxide or NO_2 as keywords and this is likely to have excluded many studies where no effects were found. The failure of studies to consistently detect an association with NO_2 reflects the small size of the effect. There is also the possibility that NO_2 is merely a marker for some other unmeasured component in the pollution mix and this is discussed further at the end of this chapter. Inconsistencies in the relationship between NO_2 and mortality might reflect inconsistencies in the relationship between NO_2 and unmeasured components of the pollution mix.

6.2.8 Interaction of NO_2 and particles

In the first APHEA study, Touloumi et al (1997) reported a tendency for the effects of NO_2 on mortality to be greater in cities with higher levels of black smoke. Stratified analysis of NO_2 effects by high or low levels of O_3 or black smoke did not, however, show significant evidence of an interaction. They noted that the short-term effects of NO_2 on mortality may be confounded by other vehicle derived pollutants. Hong et al (2002) reported a possible interaction between gaseous pollutants and PM_{10} with respect to death from stroke. Effects of NO_2 were greater at higher concentrations of PM_{10} but the effects of PM_{10} were less at high concentrations of NO_2. A Finnish study (Ponka et al, 1998) found some evidence that high concentrations of PM_{10}, O_3 and NO_2 had a further harmful additive effect beyond that associated with each pollutant individually. Similar results have not, however, been reported from other studies. More recently Katsouyanni et al (2001) have reported the results of the second APHEA study. They found that the effect of particles on mortality was markedly less when combined with low levels of nitrogen dioxide. Their results also show a slight reduction in the apparent effects of PM_{10} at high ratios of PM_{10} to NO_2 concentrations. This would be consistent with an association between NO_2 and some particle component that is particularly associated with daily mortality. In contrast, however, Samet et al (2000) show statistical results for US cities that would be consistent with PM_{10} having a greater effect on health in cities with lower mean concentrations of NO_2. The mean regression co-efficient for the effects of PM_{10} on cardiorespiratory mortality for 8 cities with annual mean concentrations of NO_2 of less than 40 μgm^{-3} was 0.88 whereas that for 8 cities with annual mean concentrations of more than 40 μgm^{-3} was 0.51. There was no correlation between concentrations of NO_2 and the regression coefficient. A similar reduction in risk at higher pollutant concentration was however seen with PM_{10} (0.96 for concentrations below 36 μgm^{-3} compared with 0.58 for higher concentrations). Concentrations of NO_2 were only moderately correlated with those of PM_{10} ($r = 0.46$). Recently, the effects of PM_{10} in this study have been recalculated and found to be smaller than originally estimated due to a flaw in the statistical programme used in the original analysis (Colburn and Johnson, 2003). The statistical flaw is unlikely, however, to be the sole cause in the differences between the European findings and the US findings which are likely also to reflect substantial differences in the pollution climate on the two continents.

A wider investigation of the relationship between PM_{10} and NO_2 was undertaken by making a cross study comparison of the studies listed in Tables 6.1-6.3. This showed that the increments in mortality risk for all cause and cardiovascular deaths associated with NO_2 or PM_{10} were not correlated with either concentrations of NO_2 or PM_{10} (Fig. 6.3). They were also independent of the ratio of NO_2 to PM_{10} concentrations. In contrast, for respiratory deaths where a significant association existed with PM_{10} (Fig 6.4), the increment in mortality risk associated with PM_{10} was moderately correlated with concentrations of NO_2 ($r>0.5$). The effects of PM_{10} appeared to be greater at higher concentrations of NO_2 which would be consistent with the findings of Katsouyanni et al (2001). The difference in findings for all cause, cardiovascular and respiratory deaths does not reflect a geographical split between European and US studies. It might indicate that NO_2 does enhance the damaging effects of PM_{10} on the respiratory system, but not the effects of PM_{10} on cardiovascular deaths.

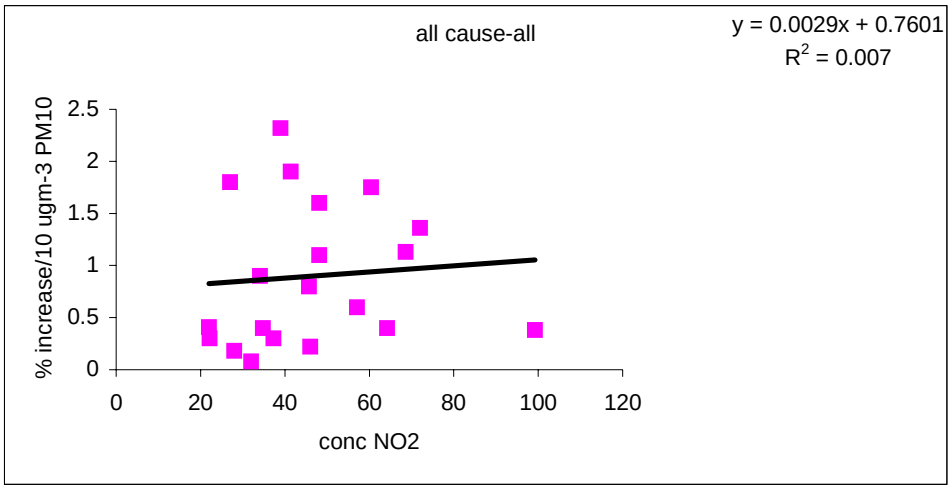

Figure 6.3: Relationship between the increment in acute mortality associated with PM_{10} and mean NO_2 concentrations in studies listed in Table 6.1 (includes both significant and non-significant associations)

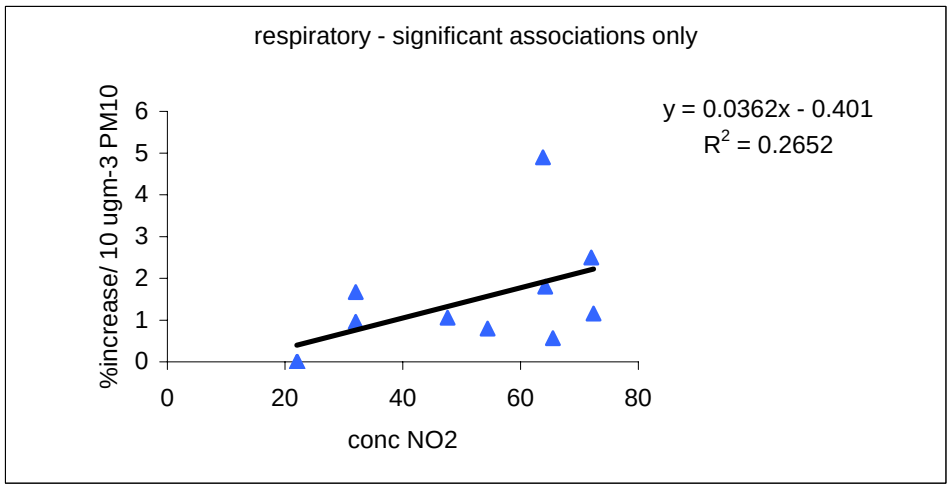

Figure 6.4: Relationship between increments in acute mortality associated with PM_{10} and nitrogen dioxide for respiratory deaths

There is no association between the size of increment in mortality risk associated with NO_2 and concentrations of PM_{10} in the studies tabulated in Tables 6.1 to 6.3 (Fig. 6.5). There is also no association between the size of the increment in mortality risk associated with NO_2 or PM_{10} and the ratio of NO_2/ PM_{10} concentrations.

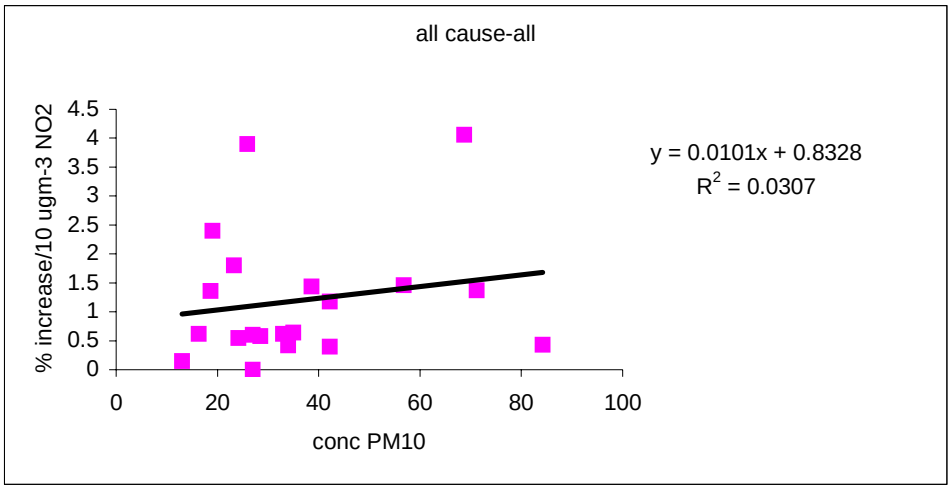

Figure 6.5: Relationship between the increment in acute mortality associated with NO_2 and mean PM_{10} concentrations in studies listed in Table 6.1 (includes both significant and non-significant associations)

6.2.9 Summary

On balance the results of epidemiological studies are suggestive of an association between NO_2 and mortality. There is much stronger evidence of an association between NO_2 and "all-cause" (nonaccidental) mortality than for specific causes but this may reflect a greater power to detect effects when a greater number of deaths is considered. The increase in daily mortality rate appears to be about 0.5% per 10 μgm^{-3} NO_2.

It appears that the combined effects of NO_2 and particle pollution are less than would be predicted from the sum of single pollutant models for NO_2 and particles. It seems highly unlikely that all of the effects of NO_2 found in epidemiological studies are attributable to concurrent exposure to PM_{10}. There is no consistent evidence that the relationship between PM_{10} and all-cause or cardiovascular mortality is modified at high concentrations of NO_2. There is limited evidence that the effects of particles on respiratory mortality may be enhanced at high concentrations of NO_2.

6.3 HOSPITAL ADMISSIONS

6.3.1 Overview

About half of the reviewed studies listed in Tables 6.7-9 found significant associations between concentrations of NO_2 and emergency hospital admission for asthma, COPD, cardiovascular illness or stroke. There is no evidence that NO_2 is more or less strongly associated with respiratory rather than cardiovascular admissions. There are many inconsistencies in the findings of different studies. Most studies of respiratory admissions have found that a 10 μgm^{-3} increase in concentrations of NO_2 is associated with increase in daily admissions of less than 2%, most commonly about 0.7%. Concentration response functions for admissions for asthma, COPD and pneumonia or respiratory infection appear to be similar to each other and to respiratory admissions more generally, although there is very little information on which to base a comparison. The findings of individual studies that have examined a more detailed breakdown of respiratory admissions are inconsistent. Schouten et al (1996), for example, found no association between NO_2 and admissions for COPD in Amsterdam but a significant association in Rotterdam.

Most studies of cardiovascular admissions have found concentration-response relationships similar to those for respiratory admission, although the results of individual studies are extremely variable. There is little concentration-response information for different categories of cardiovascular illness, but that which is available does not suggest elevated risks exist for any of the more specific conditions such as ischaemic heart disease or heart failure.

6.3.2 Lag with respect to daily concentrations

Increased hospital admissions tend to be most strongly associated with either the same day mean, or a running mean over 2, 3, 4 or 5 days for both NO_2 and PM_{10} (Table 6.10). There are no consistent differences between NO_2 and PM_{10} with respect to the lag at which the strongest associations are found. There are also no consistent differences in the lag for admissions for respiratory and those for cardiovascular illness.

Table 6.7: Hospital admission – all cause

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Buffalo, NY	all	39	24.1	32.33	52.4	**0.38** (0.15)	0.58 (0.382)	Gwynn et al (2000)
Helsinki	65+ years	39	76 TSP	19	22	**31** (3-66)	none	Ponka and Virtanen (1994)

Table 6.8: Hospital admission - respiratory

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Hong Kong	asthma (15-64 years) respiratory (65+ year)	55.9	51.8	17.7	33.5 (8hr)	none none	-1.1 (-2.4-0.1) 1.0 (0.5-1.5)	Wong et al (2002b)
London	asthma (15-64 years) respiratory (65+ years)	64.3	28.5	23.7	34.9 (8 hr)	**1.0** (0-2.04) none	1.4 (-0.1-3.0) 0.4 (-0.3-1.2)	
Brisbane, Australia	respiratory disease asthma cardiovascular respiratory – 15-64 years- all year -autumn and winter asthma – all autumn asthma - 15-64 years, winter	26.5	particle count	5.6	38	none none none 1.42 (-0.08-3.73) significant significant significant	small none none	Petrosechevsky et al (2001)
Hong Kong	Asthma in children	43.3	44.1	12.2		8	15 (inhalable fraction)	Wong et al (2001b)
Tokyo, Japan ambulance call outs for 65+ years age group	asthma acute bronchitis chronic bronchitis pneumonia	48.4	46.0	20.4	27.8	- **14** (4-24) - -	3 (1-4) - 6 (1-10) 3 (2-5)	Ye et al (2001) check
Rouen ambulance call outs	respiratory					no effect	no effect with PM_{13}	Hautemaniere et al (2000)
Los Angeles	pulmonary asthma COPD	53-78	37-54	nm	28-66	0.2 (0.2) **0.73** (0.26) **0.41** (0.21)	**0.57** (0.18) 0.3 (0.4) 0.3 (0.4)	Linn et al (2000)
Hong Kong	respiratory asthma COPD Pneumonia and	51.4	45.0	17.0	24.2	**2** (1.3-2.8) **2.6** (1.0-4.2) **2.9** (1.9-4.0)	**1.6** (1.0-2.2) **1.5** (0.2-2.8) **1.9** (1.1-2.7)	Wong et al (1999)

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
	influenza respiratory respiratory	 >51.4	 >45.0			**2.8** (1.5-4.1) 0.9 (-0.7-2.5)	**2.5** (1.4-3.6) none	
Toronto, Canada * single pollutant model ** double pollutant model	asthma obstructive lung disease respiratory infection	48	30.2	38.7	39	**0.69*** none** **0.46*** none** 1.74* 0.93**	**1.74*** 1.32** **1.36*** 1.28** **2.28*** 2.01**	Burnett et al (1999)
Buffalo, NY	respiratory	39	24.1	32.33	52.4	0.63 (0.48)	**3.186** (1.563)	Gwynn et al (2000)
London	asthma – all age asthma – 65+ years	70.9	57.2 BS	38.7	31.0	**0.66** (0.26-1.06) **1.55** (0.35-2.88)	no association **5.6** (1.09-10.31)	Anderson et al (1998)
Edinburgh	 pulmonary: 65+ years pulmonary: <65 years	50.2	20.7	22	29	 1.63 (-2.41-6.04) none	 2.1 (-3.8-8.4) 0.5 (-5.3-6.7)	Prescott et al (1998)
Sydney, Australia	asthma 1-14 years asthma 15-64 years COPD 65+ years	28.6	19.2		50	1.01 (-0.53-2.64) 0.71 (-0.92-2.42) 1.33 (-0.23-2.97)	none 0.45 (-0.81-1.05) 0.84 (-0.31-1.77)	Morgan et al (1998b)
5 European cities	respiratory: 15-64 64+ years	35-53	6-26 BS	21-66	14-60 8 hr	0.21 (-0.3-0.72) 0.38 (-0.36-1.2)	**2.8** (0.6-5.2) BS 2.0 (-0.4-4.6) BS	Spix et al (1998)
St John Canada	cardiorespiratory					none – effects with O_3 and SO_2	none	Stieb et al (2000)
4 European cities: Barcelona, Helsinki, Paris, London	asthma admissions adults (15-64 years) Barcelona Helsinki London Paris all 4 cities adults children	 53 35 69 42	 40 nm 13 28	 41 16 31 23	 72 27 40 36	 0.816 none 0.48 0.82 **0.58** (0.06-1.1) **1.6** (0.5-2.8) cold season	BS 0.72 na 0.70 0.24 0.42 (-0.3-1.14) 0.6 (-0.42-1.68)	Sunyer et al (1997)
Toronto, Canada	respiratory	73.3	28.4	20.9	82.4	1.8 (1.91)	1.64 (2.05)	Burnett et al (1997)
16 Canadian cities	respiratory diseases	67.6	CoH	38.2	65.8	none	not analysed	Burnett et al (19970
6 European cities	COPD	42-67	6-41 BS 41-155 TSP	21-53	20-69 8 hr	**0.52** (0.08-0.90)	0.66 (-1.2-1.48) TSP **0.7** (0.2-1.2) BS	Anderson et al (1997)
Birmingham	respiratory	70.9 1 hour	23.3	19.08	48 8 hr		none	EPAQS 2001

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Birmingham	Standardised hospitalisation rate for all respiratory admissions					21 (annual average)		Walters et al (1995)
Central Athens	Winter: respiratory	135	106			**1.4** (0.4-2.4)	**0.4** (0.1-0.7)	Pantazopoulou et al (1995)
	Summer: respiratory	94	111			0.4 (-0.3-0.9)	0.2 (-0.3-0.8)	
Athens area	Winter: respiratory		75				**0.7** (0.0-1.4)	
	Summer: respiratory		55				0.9 (-0.6-2.4)	
Paris, France	all respiratory	45.0	31.9 BS	29.7	27.7	0.43 (-0.03-0.90)	**0.41** (0.07-0.75)	Dab et al (1996)
	COPD				8 hour	none	none	
	asthma					**1.75** (0.59-3.04)	0.43 (-0.25-1.16)	
London	respiratory all age	71.0	14.6 BS	85.3	31.2	**0.22** (0.01-0.43)	none BS	Ponce de Leon et al (1996)
	respiratory 0-14 yr				8 hour	0.20 (-0.11-0.52)	none BS	
	respiratory 15-64 yr				41.2	0.21 (-0.05-0.60)	1.10 (-0.27-2.52) BS	
	respiratory 65+ yr				1 hour	**0.42** (0.10-0.75)	0.76 (-0.45-1.99) BS	
The Netherlands	Amsterdam	50	11 BS	28	79		BS	Schouten et al (1996)
	Respiratory 65+				1 hour	0.23 (-0.93-1.54)	1.32 (-3.13-8.67)	
	Respiratory 15-64				69	none	1.87 (-2.46-8.68)	
	COPD all age				8 hour	none	4.66 (-1.88-16.47)	
	Asthma all age					0.62 (-1.13-2.71)	none	
	Rotterdam	54	26 BS	48	76			
1977-81	Respiratory 65+				1 hour	3.42 (-0.02-8.05)	not analysed	
1982-84	Respiratory 65+				64	2.61 (-0.72-7.12)	not analysed	
1985-89	Respiratory 65+				8 hour	1.93 (-0.18-4.51)	0.94 (-1.64-4.31)	
	Respiratory 15-64					0.24 (-1.33-2.10)	3.83 (-0.09-9.32)	
	COPD all age					**2.03** (0.11-4.30)	2.41 (-1.24-7.57)	

Table 6.9: Hospital admission - Cardiovascular

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Hong Kong	cardiac Ischaemic heart disease	55.9	51.8	17.7	33.5 (8hr)	**1.4** (0.9-2.0) 0.6 (-0.2-1.4)	**0.7** (0.3-1.1) 0.5 (-0.1-1.1)	Wong et al (2002)
London	cardiac Ischaemic heart disease	64.3	28.5	23.7	34.9 (8 hr)	0.7 (0.3-1.0) 0.7 (0.2-1.2)	0.8 (0.3-1.4) 0.9 (0.1-1.6)	
Valencia, Spain	 cardiovascular heart disease cerebrovascular	66.8 24 hr 116.1 1 hr	43.7 BS	25.6	nm	1 hour mean 0.65 (-0.18-1.48) 0.85 (-0.16-1.88) **3.62** (0.66-6.67)	 1.45 (-0.04-2.97) BS 1.49 (-0.47-3.49) BS 1.56 (-1.54-4.61) BS	Ballester et al (2001)
Brisbane, Australia	cardiovascular	26.5	particle count	5.6	38	none	none	Petrosechevsky et al (2001)
Tokyo, Japan ambulance call outs for 65+ years age group	angina cardiac insufficiency myocardial infarction	48.4	46.0	20.4	27.8	**7** (4-9) **6** (3-10) **6** (3-10)	none none none	Ye et al (2001) check
Rouen ambulance call outs	cardiovascular					**1.6** (0.1-3.2)	no effect with PM_{13}	Hautemaniere et al (2000)
Los Angeles all season	cardiovascular-all cerebrovascular – all myocardial infraction congestive heart failure arrthymia stroke	53-78	37-54	nm	28-66	**0.73** (0.10) 0.21 (0.21) **0.57** (0.26) 0.52 (0.26) 0.31 (0.26) **1.05** (0.26)	**0.64** (0.12) 0.06 (0.25) 0.06 (0.3) 0.4 (0.3) 0.2 (0.3) **1.3** (0.3)	Linn et al (2000)
Hong Kong	cardiovascular heart failure ischaemic heart disease cerebrovascular cardiovascular cardiovascular	51.4 >51.4	45.0 >45.0	17.0	24.2	**1.3** (0.7-2.0) **4.4** (2.5-6.3) 1 (-0.1-2) 0.8 (-0.2-1.8) 2.0 (-1.2-1.6)	**0.6** (0.2-1.1) **4.8** (3.2-6.4) 0.7 (-0.1-1.5) 0.3 (-0.5-1.0) 0.7 (-0.5-2.0)	Wong et al (1999)
Toronto, Canada * single pollutant model ** double pollutant model	dysrythmia heart failure ischaemic heart disease cerebrovascular	48	30.2	38.7	39	1.11* none** **1.98*** 1.44** **2.03*** 1.73** **0.41*** none**	**1.66*** 0.82** **1.90*** none** **1.65*** none** none* none**	Burnett et al (1999)

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Buffalo, NY	cardiovascular	39	24.1	32.33	52.4	0.51 (0.36)	1.107 (0.906)	Gwynn et al (2000)
Edinburgh	cardiac: 65+ years cardiac: <65 years	50.2	20.7	22	29	none none	**4.8** (0.9-8.9) 0.8 (-5.2-7.2)	Prescott et al (1998)
Sydney, Australia	heart disease all heart disease 65+ yrs heart disease <65 yrs	28.6	19.2		50	**1.88** (1.12-2.65) **2.07** (1.31-2.85) **1.48** (0.36-2.63)	**0.77** (0.21-1.35) **0.98** (0.31-1.66) 0.35 (-0.59-1.32)	Morgan et al (1998b)
London	 myocardial infarction angina other ischaemic arrhythmia heart failure cerebrovascular other circulatory combined circulatory	66.7	BS 12	15.9	26	 **0.48** (0.15-0.84) 0.37 (-0.09-0.80) none **0.48** (0.01-1.72) none none **0.32** (0.00-0.70) **0.43** (0.09-0.78)	BS **2.02** (0.61-3.52) **2.02** (0.20-3.95) none 1.69 (-0.28-3.80) 0.53 (-1.03-2.06) none 1.05 (-0.39-2.57) **1.59** (0.19-3.09)	Polonieki et al 1997
3 US Counties Cook Los Angelos Mari Cook Los Angelos Mari	 cardiovascular cerebrovascular	 47.6 72.4 36.2	 35 44 41	 15.9 5.3 5.3	 36 48 50	 1.52 (5.36) 1.26 (9.18) 1.60 (2.26) 0.99 (2.58) 0.60 (3.14) none	 0.84 (2.72) 0.64 (1.24) none 0.64 (1.44) 0.2 (0.28) **0.2** (0.08)	Moolgavkar (2000b)
St John Canada	cardiorespiratory					none – effects with O_3 and SO_2	none	Stieb et al (2000)
Toronto, Canada	cardiovascular	73.3	28.4	20.9	82.4	1.84 (1.16)	1.27 (0.99)	Burnett et al (1997)
10 Canadian cities – elderly patients	congestive heart failure					strongest association with carbon monoxide		Burnett et al (1997)
Tuscon	cardiovascular disease	37.8	39	8.5	53.8	0.32 (-0.21-1.75)	**0.88** (0.15-1.53)	Schwartz (1997)
Birmingham	cardiovascular	70.9 1 hour	23.3	19.08	48 8 hr		0.7 (-0.3-1.3)	EPAQS 2001
Central Athens Athens area	Winter: cardiac Summer: cardiac Winter: cardiac Summer: cardiac	135 94	106 111 75 55			**1.5** (0.4-2.5) none	**0.5** (0.2-0.8) 0.2 (-0.2-0.7) **1.1** (0.4-1.8) 0.3 (-1.1-1.6)	Pantazopoulou et al (1995)
Helsinki	short term ischaemic long term ischaemic cerebrovascular					2.34 (1.1) 1.62 (0.61)	 1.61 (0.89)	Ponka and Virtanen (1996)

Location	*Type of admission*	*Mean concentrations (µgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 µgm^{-3})*	*PM_{10} (10 µgm^{-3})*	
7 US cities	congestive heart failure	1 hour		1 hour	I hour			Morris et al (1995)
Los Angeles		147		26	150	0.26 (0.52-1.00)	not analysed	
Chicago		86		66	78	**0.89** (0.37-1.42)		
Philadelphia		103		77	90	0.16 (-0.26-0.63)		
New York		122		85	82	**0.37** (0.10-0.68)		
Detroit		78		66	78	0.21 (-0.41-0.94)		
Houston		78		48	104	none		
Milwaukee		76		45	92	0.26 (-0.57-1.21)		

Table 6.10: Lag between pollutant concentrations and effects in studies of hospital admission

Study	*Cause of admission*	*NO_2*	*PM_{10}*
Wong et al 2002	Hong Kong		
	respiratory	0	0
	cardiac	0	0
	ischaemic heart disease	3	2
	London		
	asthma	2	2
	respiratory	3	3
	cardiac	0	0
	ischaemic heart disease	0	3
Petrosechevsky et al (2001)	respiratory 15-64 years	0	0-4 particles
Ballester et al (2001)	all cardiovascular	0 1 hr	2 BS
	heart disease	2	2
	cerebrovascular	4	5
Linn et al (2000)	cardiovascular, pulmonary, cerebrovascular, all non accidental	0	0
Moolgavkar (2000)	cardiovascular	0	0
	cerebrovascular	0	0
Wong et al (1999)	respiratory – all	0-3	0-3
	cardiovascular -all	0-1	0-2
	asthma	0-3	0-3
	COPD	0-3	0-3
	pneumonia and influenza	0-3	0-3
	heart failure	0-3	0-3
	ischaemic heart disease	0-1	0-1
	cerebrovascular	0-1	2
Burnett et al (1999)	asthma	0	0-2
	obstructive lung disease	0	0-1
	respiratory infection	0	0-2
	dysrythmia	0-2	0
	heart failure	0	0-2
	ischaemic heart disease	0-1	0-2
	cerebrovascular	0	-
Morgan et al (1998)	asthma, COPD, heart disease	0	0
Prescott et al (1998)	cardiac, respiratory	0-2	0-2
Sunyer et al (1997)	asthma		
	Barcelona	0	3
	London	0	0
	Paris	1	0
Dab et al (1996)	respiratory	0	0
	COPD	2	2
	asthma	0-1	0
Schouten et al (1996)	respiratory, all ages (inconsistent by age and more detailed breakdown of cause)	0	2
Ponce de Leon et al (1996)	respiratory	2	1
Ponka and Virtanen (1996)	short term ischaemic illness	6	
	long term ischaemic illness		6
	cerebrovascular	6	
Ponka and Virtanen (1994)	65+ years	6	-

6.3.3 Vulnerable populations

The results of several studies suggest that the effects of NO_2 on the risk of emergency hospital admission are greater in 65+ years age group, although the increase in risk generally lacks statistical significance (Anderson et al, 1998; Wong et al 1999; Prescott et al 1998; Spix et al, 1998; Atkinson et al, 1999a, Morgan et al, 1998; Schouten et al, 1996; Ponce de Leon et al, 1996). Other studies have not found evidence of increased risk for older people (Wong et al, 2002).

6.3.4 Seasonal effects

A number of studies have found that NO_2 has a greater effect on hospital admission for respiratory illnesses during the winter than during the summer (for example, Petroechevsky et al 2001; Pantazopoulou et al, 1995; Schouten et al 1996). Pantazopoulou et al (1995) also found that NO_2 had a greater effect on cardiovascular admissions in winter. Other studies have found inconsistent seasonal effects. Linn et al (2000) found that the association between hospital admissions and NO_2 was only significant for respiratory admissions during the autumn and winter whereas for cardiovascular admissions it was significant during the summer, autumn and winter and for cerebrovascular admissions it was significant only during the spring. Schouten et al (1996) found inconsistent seasonal effects when they examined different subcategories of respiratory admission. Anderson et al (1998) found that effects greatest in warm season for all ages but greatest in cool season for 65+ years age group. Anderson et al (1997) found that effects on COPD admission were marginally greater in the warm season than in the cool season. Ponce de Leon et al (1996) found that the apparent effects of NO_2 on respiratory admissions were slightly greater in the warm season than during the winter but attributed this difference to possible confounding by ozone. Burnett et al (1997) found that the risks of hospital admission associated with NO_2 increased slightly when temperature and relative humidity were included in the model.

Overall it is difficult to determine whether temperature significantly affects vulnerability to NO_2 pollution, or whether apparent seasonal variability may indeed reflect inadequate control for the confounding effects of temperature or other pollutants such as ozone that show seasonal variability in their concentrations. Some of the inconsistencies may reflect the small size of any effect with NO_2.

6.3.5 Evidence for an independent effect of NO_2

Most recent studies have highlighted the importance of particles in the association between air pollution and hospital admissions. Burnett et al (1997), however, believed that the apparent association of emergency hospital admission with various particle indices was explicable in terms of concurrent exposure to oxidant gases rather than due to particle exposure. Subsequent publications by the same group, however, appear to acknowledge the potential role of particles in the association between air pollution and health.

In most studies where significant effects have been found, concentrations of NO_2 were strongly correlated with those of PM_{10}. Morgan et al (1998b), however, do report a significant association between NO_2 and admissions for heart disease in the absence of a strong correlation between NO_2 and particles. Similarly Ballester et al (2000) found an significant association between admissions for cerebrovascular disease and NO_2 in the absence of a strong correlation between concentrations of NO_2 and particles. Ballester et al (2001), however, found little evidence that the apparent effect of NO_2 on hospital admission for cardiovascular and heart disease was independent of that of other pollutants. Ponce de Leon et al (1996) found a significant association between NO_2 and respiratory admissions in the absence of a strong correlation between NO_2 and black smoke. For the reviewed studies as a group, mean concentrations of NO_2 and PM_{10} were strongly correlated in studies of cardiovascular and all respiratory admissions but only weakly correlated in studies that specifically considered asthma ($r = 0.46$). This is possibly due to studies being conducted to specifically investigate the widely reported association between asthmatic attacks and ozone and the likelihood that high ozone concentrations will arise in conjunction with high particle concentrations but lowered concentrations of NO_2. The increments in risk of admission for cardiovascular or respiratory illness associated with PM_{10} are not correlated with those associated with NO_2 whereas for asthma the increments associated with NO_2 and PM_{10} are strongly correlated ($r=0.92$).

A number of investigators have compared the apparent effects of NO_2 and PM_{10} in single and multipollutant models. Burnett et al (1999) found that in multipollutant models, the effect of NO_2 is reduced if the particle metric is $PM_{2.5}$ rather than PM_{10}. The apparent effects of NO_2 largely disappeared in multipollutant models whereas that of PM_{10} was only slightly reduced. Moolgavkar (2000) found that for one of three US counties, the apparent effect of PM_{10} on admission for cardiovascular disease was reduced substantially in a two pollutant model with NO_2 whereas the effect of NO_2 was only slightly changed by the addition of PM_{10} to the model. Morgan et al (1998) found that the effects of particulate on admissions for COPD or heart disease in the over 65s was substantially reduced in multipollutant models particularly for heart disease and COPD. The apparent effects of NO_2 were, however, increased for asthma admissions for children in multipollutant models. In contrast, Anderson et al (1998) found that the inclusion of black smoke in a two pollutant model did not substantially affect the apparent effect of NO_2 on admissions for asthma when all age groups were included in the analysis. The apparent effects of NO_2 appeared to increase, however, when only children were included in the analysis. Ponka and Virtanen (1996) found no evidence of a reduced effect of NO_2 or particles in multipollutant models. Schouten et al (1996) report that there was little difference in the apparent effects of individual pollutants on respiratory admissions in single or multipollutant models. Overall the results of the various analyses that have used multipollutant models do not strongly suggest that the apparent effect of NO_2 in single pollutant models is entirely explicable in terms of concurrent exposures to particles or other pollutants.

In addition to potential confounding by PM_{10}, the presence of other pollutants such as ozone and allergens such as pollen may also obscure the relationship between NO_2 and the risk of hospital admission, particularly for respiratory illness. Rosas et al (1998) found that emergency admissions for asthma in a hospital in Mexico City were more strongly associated with aeroallergens than air pollutants. In general, however, concentrations of NO_2 and ozone are negatively correlated such that confounding is unlikely to be a major problem in epidemiological studies. There is also no reason to expect concentrations of pollen or fungal spores to covary with concentrations of NO_2. Anderson et al (1998) found evidence that NO_2 as well as SO_2, O_3 and particles were significantly associated with hospital admissions for asthma with little evidence of confounding by pollen. Confounding by other traffic generated pollutants may, however, obscure relationships with NO_2 in studies of hospital admissions. Both Burnett et al (1999) and Linn et al (2000) reported difficulty in distinguishing the effects of NO_2 from those of carbon monoxide. Morris et al (1995) found that while NO_2 appeared to have significant effects on hospital admissions for congestive heart failure in a single pollutant model, these effects largely disappeared in multipollutant models with other gaseous pollutants. Carbon monoxide emerged as the only pollutant to have a significant association with admissions for congestive heart failure in these multipollutant models, but particles were not included in the analysis.

6.3.6 Interaction of NO_2 and particles

There is relatively little information about the interaction between NO_2 and particles. Many of the hospital admission studies reviewed used black smoke as a measure of particle concentrations rather than PM_{10}. The two measures are not directly comparable. Spix et al (1998) reported that the effects of black smoke on respiratory admissions in some European cities was significantly stronger on days of high NO_2 levels although NO_2 was not itself associated with admissions. This is consistent with the subsequent findings for mortality in European cities in the APHEA 2 study (Katsouyanni et al, 2001). For the reviewed studies as a group, the increments in risk of admission for cardiovascular or respiratory illness associated with PM_{10} were not correlated with those associated with NO_2 whereas for asthma the increments associated with NO_2 and PM_{10} are strongly correlated with each other (Fig. 6.6; r=0.92). The relationship between these two parameters is much weaker, if a single study

in which particularly steep concentration-response functions were reported for both NO_2 and PM_{10} is excluded from consideration.

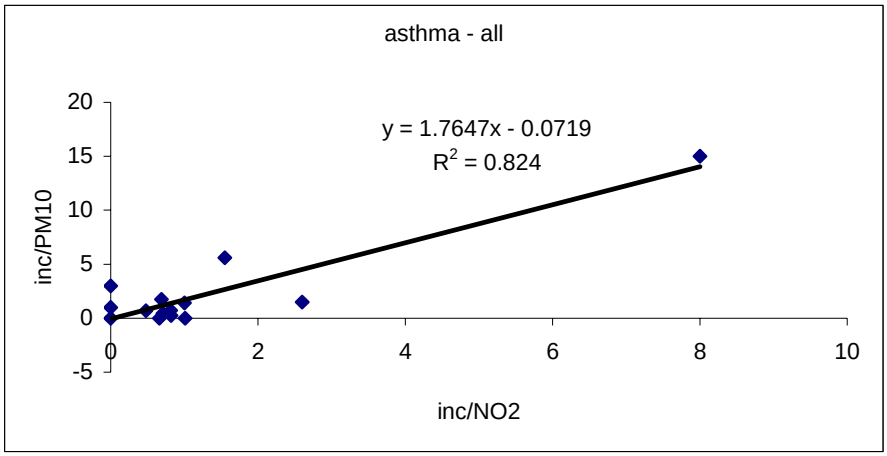

Figure 6.6: Relationship between increment in risk associated with NO_2 and that associated with PM_{10} in studies of hospital admission for asthma (includes both significant and non-significant associations)

The increments in risk for cardiovascular, respiratory or asthma admissions associated with NO_2 or particles were not correlated with concentrations of NO_2 or PM_{10} (Fig 6.7). The reviewed studies, as group, therefore do not provide evidence that the risks of admission associated with either NO_2 or PM_{10} are modified in the presence of high concentrations of the other pollutant. It is possible, however, that any effect that may exist for hospital admissions has been obscured because of differences in the exact health endpoint considered (for example, admissions for COPD versus all respiratory admissions). Any relationship may also have been obscured by the inclusion of a large proportion of studies where the particles metric was black smoke rather than PM_{10}.

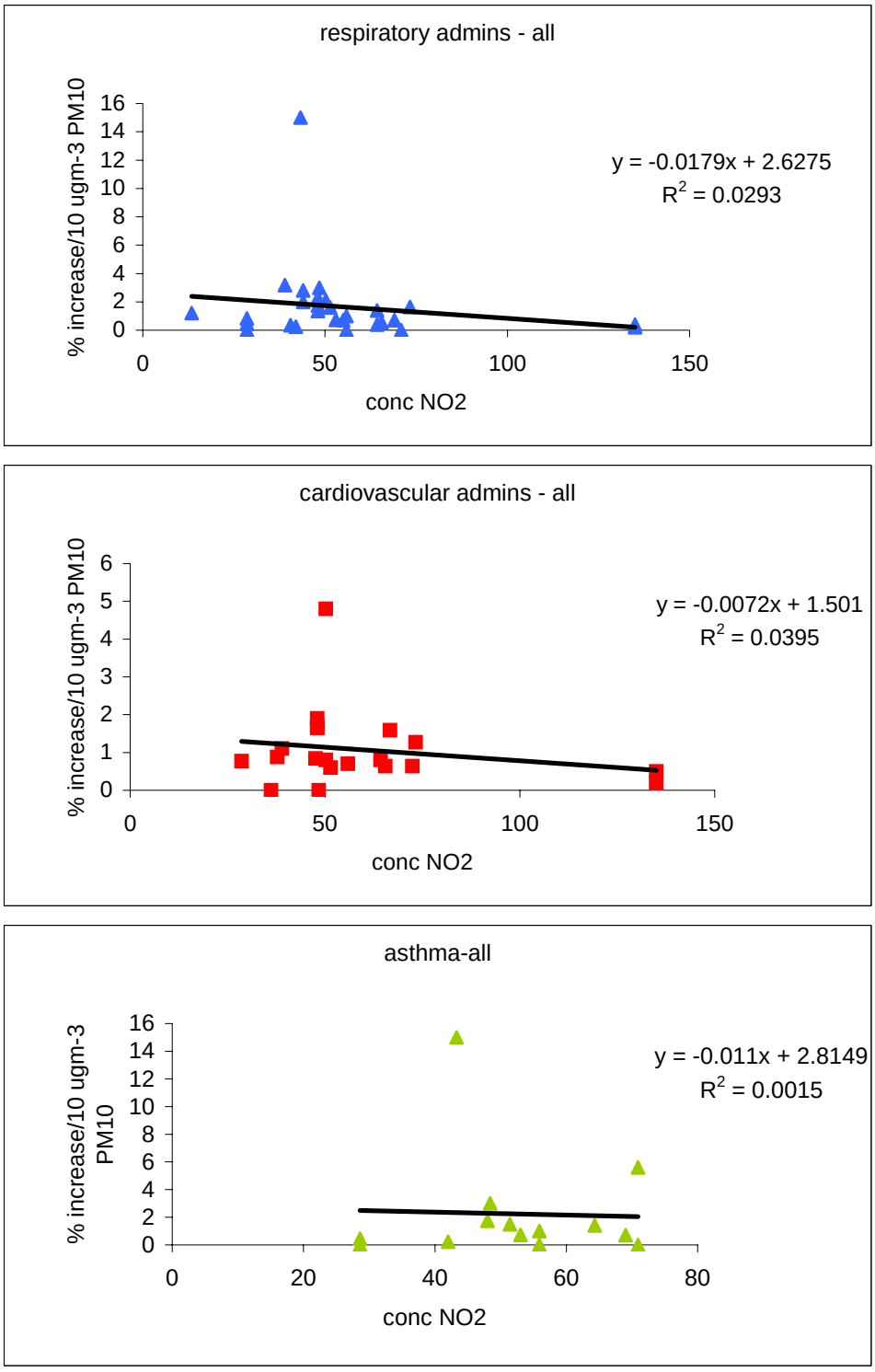

Figure 6.7: Relationship between concentrations of NO_2 and the predicted increase in hospital admissions for various causes associated with PM_{10} (includes both significant and non-significant associations)

6.3.7 Summary

Overall, the evidence linking NO_2 to increased levels of hospital admission is weaker than that linking NO_2 to increased daily mortality. Hospital admissions for either respiratory or cardiac illness may increase by about 0.7% per 10 μgm^{-3} NO_2.

6.4 EMERGENCY HOSPITAL VISITS

6.4.1 Size of effect

About half of the relatively small number of studies of the relationship between air quality and emergency hospital visits have found a significant association between emergency visits for asthma and NO_2 (Table 6.11). The apparent magnitude of the effect of NO_2 varies between studies with reported concentration-response relationships ranging from less than 0.1 to 7.6% per 10 μgm^{-3}. The apparent effect is generally slightly greater than that found for emergency hospital admission.

6.4.2 Lag with respect to pollutant concentrations

The reported lag between elevated concentrations of NO_2 and/or particles and effects is appears to be generally small, although information is limited. The association between pollutant and effect is generally strongest for the same day concentration or the 4 day mean concentration (Table 6.12).

Table 6.12: Lag between pollutant concentrations and emergency hospital visits

Study	***Cause of admission***	***NO_2***	***PM_{10}***
Thompson et al (2001)	acute asthma in children	0-3	0-1
Atkinson et al (1999)	A&E visits all respiratory illness		
	all age	1	1
	children	1	1
	adults	2	2
	elderly	0	1
	A&E visits asthma		
	all age	0	1
	children	1	2
	adults	1	1
Braga et al (2001)	respiratory illness in children	0-4	0-4
Tenias et al (1998)	asthma (visits)	0	0
Castellasague et al (1995)	emergency visits for asthma	0-3	0-3

Table 6.11: Emergency visits

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
London	A&E visits all respiratory complaints all age children adults elderly asthma all age children adults					 0.06 (-0.03-0.16) 0.11 (-0.03-0.26) 0.10 (-0.04-0.24) **0.21** (0.03-0.4) **0.23** (0.07-0.4) **0.47** (0.23-0.73) **0.23** (0.01-0.47)	 0.10 (0.03-0.17) 0.13 (0.02-0.17) 0.17 (0.07-0.27) none **0.17** (0.06-0.29) **0.15** (0.0-0.31) **0.26** (0.09-0.43)	Atkinson et al (1999b)
Valencia Spain	asthma (visits)	57.7	38.8 BS	26.6	62.8 I hr	**7.6** (2-13.4)	2.5 (-1.9-7.2)	Tenias et al (1998)
Israel, children	Emergency room visits for asthma					significant relationship. CR not quantified	na	Garty et al (1998)
Sao Paulo, Brazil	emergency visits for respiratory illness in children and adolescents	141.4	66.5	21.4	65.0	**0.81** (0.41-1.21)	**2.0** (1.63-2.34)	Braga et al (2001)
Santa Clara County, California (residental wood burning major source of particles)	emergency room visits for asthma	131.4 I hour	61.2		48 1 hour	not analysed	20^oF 6 (2-10) 30^oF 4 (2-6) 41^oF 2 (0-3)	Lipsett et al (1997)
Oulu, northern Finland	Emergency room visits all same week asthma same week asthma week after	13.4 (38.5 daily max)	18.3 TSP	10.0		 0.3 ns **4.2** (p<0.001) **5.8** (p<0.001)	TSP 1.7 ns **2.4** (p<0.05) 2.0 ns	Rossi et al (1993)
Seatle	emergency hospital visits for asthma in children					none	13.6 (7.3-20.9) $PM_{2.5}$	Norris et al (1999)
Barcelona	Emergency room visits for asthma summer winter	100.8	68 BS	52	56.6	 **2.8** (0.4-5.2) 2.9 (-0.0-0.3)	BS **4.6** (0.4-6.4) 0.9 (-0.8-2.6)	Castellague et al (1995)

Location	*Type of admission*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Belfast, Northern Ireland, children	acute asthma exacerbations	40.5	28.4	43.7	35.8	**4.2**0 (2.62-8.92)	about 0.35 10 (3-16)/doubling in concentration of PM_{10}	Thompson et al (2001)
St John, New Brunswick, Canada	asthma emergency department visits	48	36.7 TSP	101	83.2	none	none	Stieb et al (1996)
Sao Paulo, Brazil	emergency room visits for pneumonia and influenza					no effects	no effects	Martins et al (2002) – English abstract listed by Medline
Central Athens Athens area	Winter Summer Winter Summer	135 94	106 111 75 55			**8.8** (2.6-15.0) 2.0 (-3.2-71.8)	1.7 (-0.4-3.7) 2.4 (-1.4-6.2) 2.6 (-1.2-6.4) 1.3 (-10.9-13.6)	Pantazopoulou et al (1995)

6.4.3 Factors affecting apparent concentration-response relationships

There is limited evidence to suggest that NO_2 has a greater effect on emergency hospital visits for respiratory illnesses during the winter than during the summer. Homen et al (1997) found significant relationships between emergency hospital visits for acute asthma and NO_2 for children on cold days (study not shown in Table 6.11 because results not expressed as a concentration-response function). Similarly Rossi et al (1993) found that the effect of NO_2 on emergency room visits for asthma was greater in the winter than during the summer. Local pollution mix may have an important confounding effect on apparent effects as summertime concentrations of ozone will be much greater in warm sunny climates than in colder wetter places.

There is also limited evidence to suggest that the effects of NO_2 on the risks of A&E visits for respiratory illness or asthma are much greater for children than for adults of working age (Atkinson et al, 1999, Morgan et al, 1998; Holmen et al, 1997). Braga et al (2001) found that the effects of NO_2 on hospital admissions for respiratory illness in children was greatest in children under 3 years in age and least in children of 14-19 years. The effect of PM_{10} was similarly greatest on admissions for the under 3s but was greater for adolescents over 13 than for children between 3 and 13 years in age. There were substantial differences in the types of illness leading to admissions in children of different ages. Over 70% of admissions for young children were for pneumonia or bronchopneumonia whereas only about 31% of admissions for 14-19 year olds were for these causes and over 50% of admissions were for respiratory illnesses of causes other than upper respiratory tract infection, acute bronchitis or asthma or pneumonia. The authors suggested that the apparent greater vulnerability of adolescents to the effects of air pollution than younger children was due to the effects of pyschosocial factors (many would be in paid employment and also studying) and hormonal changes leading to reduced immune activity. In addition, smoking in this age group may have increased vulnerability to the effects of air pollution.

Norris et al (1999) found a substantial difference in hospitalisation rates for childhood asthma between children in the inner city and those living in the suburbs (>600/ 100 000 vs <100/100000). Air pollution would however be only one of many potential causes of this difference.

6.4.4 Interaction between NO_2 and particles and evidence for an independent effect with NO_2

There is very little information about the potential interaction of NO_2 and particles with respect to emergency hospital visits. As with other health endpoints, the strong correlation between NO_2 and particles as PM_{10} or black smoke makes the identification of an independent role for NO_2 difficult (for example, see Thompson et al, 2001). It is also difficult to separate the effects of NO_2 specifically from those of traffic pollution more generally. Thompson et al (2001) found that the apparent effect of NO_2 on emergency asthma visits in children was increased by nearly 40% when the model was adjusted to allow for the benzene level, which would be a good proxy for traffic fumes. Relatively few investigators have investigated the effects of NO_2 and PM_{10} in multipollutant models. Atkinson et al (1999b) found that for visits to A&E for asthma in children, the apparent effect of NO_2 was reduced from 8.97 to 6.95 for 69 μgm^{-3} increase in NO_2 when PM_{10} was included in the model. Similarly the effect of PM_{10} was reduced from 7.41 to 4.72 for a 30.7 μgm^{-3} increase in PM_{10} when NO_2 was included in the model. The inclusion of black smoke in the model did not greatly affect the apparent effect of NO_2, although the inclusion of NO_2 reduced the apparent effect of black smoke. More generally, across the reviewed studies there were no consistent relationships between the increments in risk found with NO_2 or PM_{10} and concentrations of NO_2 or PM_{10} (Fig. 6.8). There was also no relationship between the increments in risk found with NO_2 and those

found with PM_{10} (Fig. 6.9). Inconsistencies in averaging times for pollutant concentrations may have concealed any relationships that may exist.

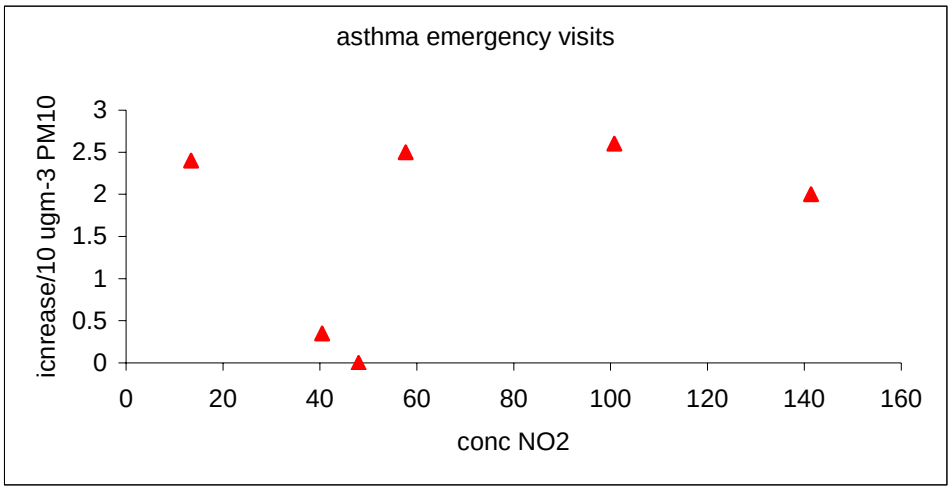

Figure 6.8: relationship between concentrations of NO_2 and the increased risk of emergency hospital visits for asthma associated with PM_{10}.

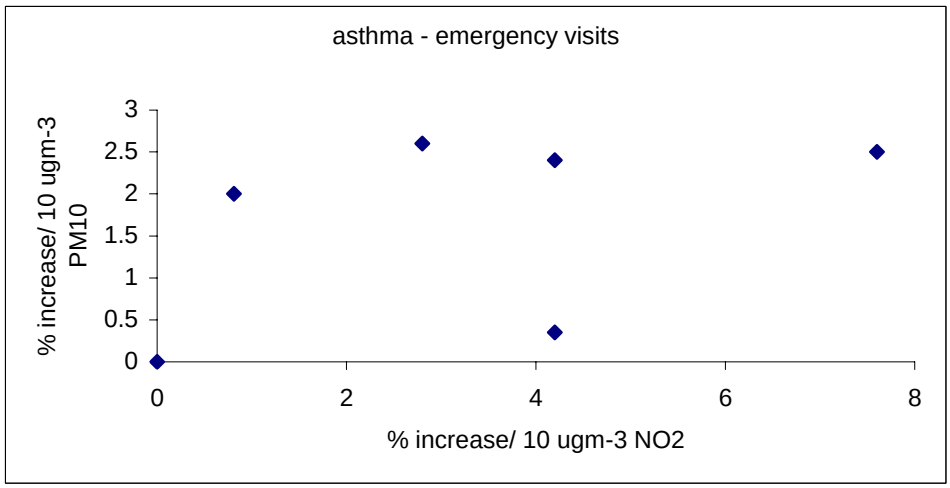

Figure 6.9: Relationship between increased risk of emergency visits for asthma associated with NO_2 and the risk associated with PM_{10}

6.4.5 Other confounding factors

Nitrogen dioxide and PM_{10} are only two of many factors that may be associated with the exacerbation of asthma leading to emergency hospital visits. Fauroux et al (2000), for example, found an association between ozone and emergency room visits for asthma in a children's hospital in Paris, but no association with NO_2 or particles. Dales et al (2000) reported that airborne fungal spores account for a significant proportion of the asthma exacerbations in children that give rise to an emergency department visit. Lewis et al (2000) found that ambient levels of chemical pollutants including NO_2 were not associated with emergency hospital attendance for asthma. The results of human volunteer experiments suggest that NO_2 is likely to enhance the response of asthmatics to allergens such as pollens. There is little supporting epidemiological evidence, but this may reflect an absence of studies rather than absence of effect. Garty et al (1998) noted the confounding effects of stress on exacerbations of asthma in children leading to emergency room visits.

6.4.6 Conclusions

Overall, it seems likely that NO_2 is associated with some increase in emergency hospital visits for asthma but the scale of the effect is difficult to assess. It is probably less than 1% per 10 μgm^{-3}, but some studies report much greater effects. Apparent effects are generally greater in children than for the population as a whole. At least some of the effects attributed to NO_2 in epidemiological studies may be explicable in terms of concurrent exposure to particles rather than a specific association with NO_2. The potential interaction between NO_2 and airborne allergens has not been fully investigated.

6.5 GP CONSULTATIONS, CLINIC VISITS, GP HOME VISITS

6.5.1 Size of effect

Several studies have found statistically significant associations between NO_2 and clinic visits or GP consultations including home visits for respiratory illness (Table 6.13). A statistically significant association has also been found between NO_2 and GP home visits for cardiovascular illness. The size of the apparent effects of NO_2 on GP consultations or clinic visits found in different studies is variable, but is generally between 1 and 1.5%/10 μgm^{-3} NO_2. This is similar to the size of effect found for emergency hospital visits for asthma.

6.5.2 Lag with respect to NO_2 concentrations

There are too few studies to determine whether these measures of respiratory and cardiovascular health are most strongly associated with the same day concentrations of NO_2 or with those on days immediately previous to the consultation (Table 6.14). Hwang et al (2002) found that pollution related effects on clinic attendance for lower respiratory illness decreased with increasing time lag. Ilabaca et al (1999) found that patients generally reported having waited for 2 to 3 days before attending the emergency room which would be consistent with symptoms being initiated on the day on which peak pollution levels occurred.

Table 6.14: lag between pollutant concentrations and effects in reviewed studies

Study	***Endpoint***	***NO_2***	***PM_{10}***
Hajat et al (2002)	GP consultations: upper respiratory illness	2	2
Hajat et al (1999)	GP consultations: asthma lower respiratory illness	0 1	2 2
Medina et al (1997)	Doctors house calls: asthma cardiovascular angina/ myocardial infarction headache	0-3 0 2 1	0-3* 2** 1* 1** 3* - 1* 1**
Hernandez Garduno et al (1997)	Clinic visits for upper respiratory tract infections all age 0-14 years	 0 0	
Ilabaca et al (1999)	Children – Emergency Visits respiratory illness – cold season respiratory illness – warm season upper respiratory illness – cold season pneumonia – cold season upper respiratory illness – warm season pneumonia – warm season	 2 3 2 0-6 3 0-6	 0-6 3 0-6 0-6 3 0-6
Hwang and Chan (2002)	Clinic visits for lower respiratory tract illness	0	0

**Black smoke; ** PM_{13}*

Table 6.13: GP Consultations, Clinic visits etc

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Taiwan	clinic visits for lower respiratory tract illness 0-14 years 15-64 years 65+ years all	45	58.9	14.3	108	 **2.85** (2.19-3.50) **3.28** (2.85-3.94) **3.94** (3.07-1.75) **3.07** (2.63-3.50)	 **0.87** (0.34-4.72) **1.02** (0.34-1.53) **1.36** (0.68-1.86) **0.85** (0.34-4.72)	Hwang et al (2002)
Santiago, Chile children	emergency visits for respiratory illness all -cold season all – warm season upper respiratory-cold upper respiratory-warm pneumonia – cold pneumonia -warm	 160.2 97.0	 123.9 80.3	 31.8 14.9	 27.6 66.6 1 hr	 **0.67** (0.37-0.97) **1.31** (0.60-2.03) **1.01** (0.60-1.42) **1.41** (0.52-2.32) **1.67** (0.18-3.23) **4.80** (0.31-9.75)	 **0.61** (0.22-1.01) **0.63** (0.02-1.25) **0.89** (0.35-1.43) **0.71** (-0.66-1.49) **1.45** (0.24-2.74) **5.65** (1.22-10.5)	Ilabaca et al (1999)
Sao Paulo, Brazil	emergency visits for respiratory illness in children respiratory illness lower respiratory upper respiratory wheezing	163	65	20	67	 **0.3** (0.1-0.5) none 0.3 (-0.1-0.7) none	 **4.0** (3.4-4.6) **4.2** (2.4-6.0) 3.9 (-0.4-2.3) **2.9** (1.3-4.6)	Lin et al (1999) (unclear what interval relative risks are cited for)
Le Harve, France	sales of respiratory drugs					check		Zeghnoun et al (1999)
London	GP consultations upper respiratory 0-14 years 15-64 years 65+ years	64	28.5	21.2	35 8 hr	 0.31 (-0.05-0.67) **0.80** (0.31-1.30) **1.36** (0.59-2.16)	 0.63 (-0.06-1.31) **1.78** (0.91-2.69) **3.19** (1.66-4.78)	Hajat et al (2002)
London	GP consultations asthma lower respiratory	87.8	46.9	88.2	46.8	 1.90 (-0.63-4.44) **1.18** (0.36-2.72)	 0.98 (-0.12-2.07) **0.64** (0.12-1.16)	Hajat et al (1999)

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*			*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*		
Greater Paris, France	Doctors House Calls asthma all age 0-14 years 15-64 years cardiovascular angina/ myocardial infarction headache eye conditions	56 24 hour 87 1 hour	BS 21 PM_{13} 25	19	34 8 hour 44 1 hour	 **4.1** (2.6-5.4) **5.4** (2.2-8.7) **3.2** (1.5-4.8) **0.9** (0.2-1.5) 4.1 (-0.4-9.6) **2.2** (1.5-2.8) none	BS **2.0** (0.9-3.4) **7.3** (3.9-10.7) 0.9 (-0.4-2.3) 0.4 (-0.2-1.1) 1.8 (-1.6-5.9) **3.6** (2.7-4.3) none	PM_{13} **2.5** (1.0-4.0) **8.0** (4.0-12.8) 1.2 (-0.5-3.2) **0.8** (0-1.5) none **3.2** (2.5-4.2) none	Medina et al (1997)
Mexico City	upper respiratory tract infections: clinic visits all age 0-14 years 15+ years	about 140 1 hour	nm		about 240 1 hour	 **1.15** (0.30) **0.75** (0.18) **0.40** (0.10)	 not analysed not analysed not analysed		Hernandez Garduno et al (1997)
Copenhagen Children	contacts with emergency medical services for respiratory illness	68	22 BS	18	11	**0.25**			Keiding et al (1995)

6.5.3 Vulnerable groups

There is limited information to suggest that the effects of NO_2 on GP consultations, clinic visits and GP home visits are greater for children and the elderly than for those of working age.

Hwang et al (2002) found that the effects of NO_2 on clinic visits for lower respiratory illness were greatest for those over 65 years in age. In contrast, Hajat et al (1997) found that the effects of NO_2 on GP consultations for lower respiratory symptoms were least for those over 64 years and greatest for those under 15 years, but the effects of PM_{10} were greatest for those over 64 years. More recently Hajat et al (1997) found that the effects of both NO_2 and PM_{10} on consultations for upper respiratory illness and asthma were greatest for those over 64 years. Medina et al (1997) found that the effects of NO_2, black smoke and PM_{13} on GP home visits for asthma was greatest for those under 15. Hernandez Garduno et al (1997) found that the effects of NO_2 on clinic visits for respiratory illness were greater for those under 15 than older patients.

6.5.4 Interaction between air pollution and other factors affecting respiratory health

Several community specific variables such as community population density and annual mean concentrations of air pollution have been found to have a modifying effect on the relationship between clinic visits for lower respiratory tract illness and air pollution (Hwang et al, 2002). Hajat et al (2002) found that the effects of NO_2 on GP consultations for upper respiratory symptoms were greater in the winter than the summer for those over 64 years but the reverse was true of younger patients. The effects of PM_{10} were greatest in the winter for both the under 15s and the over 65s. Ilabaca et al (1999) found that the effects of NO_2 on emergency room visits for respiratory illness were greater in the warm season than in the cold season, but the same was not true for PM_{10}. Levels of air pollution were very much higher during the cold season than during the warm season.

6.5.5 Evidence for an independent effect with NO_2

The reviewed studies included several in which concentrations of NO_2 and PM_{10} were strongly correlated (Hwang and Chan, 2002; Ilabaca et al, 1999, Medina et al, 1997) and others in which concentrations of NO_2 and PM_{10} or black smoke were relatively poorly correlated (Lin et al, 1999; Keiding et al, 1995). Lin et al (1999) found a small but statistically significant increased risk of respiratory illness in children associated with NO_2, even in the absence of a strong correlation between concentrations of NO_2 and particles. Two authors have found evidence to suggest that the apparent effects of NO_2 in single pollutant models may be partly or largely due to concurrent exposure to PM_{10}. Lin et al (1999) found that the apparent effects of NO_2 on emergency hospital visits for respiratory illness in children disappeared in multipollutant models whereas the apparent effects of PM_{10} were slightly increased. Ilabaca et al (1999) found that the apparent effects of PM_{10} on emergency room visits were similar in single and multipollutant models whereas those of the gaseous pollutants were much reduced in multipollutant models. Overall, it is unclear whether the apparent effects of NO_2 on GP consultation and clinic visits that have been reported in epidemiological studies are actually attributable to NO_2 as opposed to other pollutants.

6.5.6 Conclusions

Several studies have reported associations between concentrations of NO_2 on the same day or up to 6 days earlier and clinic visits or GP consultations, including home visits for respiratory illness. The size of the apparent effects of NO_2 on GP consultations or clinic visits found in

different studies is very variable, but is generally about 0.23%/10 μgm^{-3} NO_2. Effects are greatest in children and in the elderly. The importance of other pollutants in the apparent relationships between NO_2 and primary healthcare usage is unclear and it is possible that effects are largely due to concurrent exposure to particles.

6.6 RESPIRATORY SYMPTOMS

6.6.1 Overview

There have been a large number of studies of the association between NO_2 and respiratory symptoms in children and a few studies of respiratory symptoms in adults with asthma or other respiratory illness. There is very little information about effects in healthy adults. Most of the studies reviewed also considered particles. Exposure to environmental tobacco smoke is likely to be a major confounder and may have substantially weakened the power of epidemiological studies to detect effects.

6.6.2 Children

Of the large number of studies of the relationship between ambient NO_2 and respiratory symptoms in children (Table 6.15), only a few have found statistically significant effects (Linaker et al, 2000b; Boezen et al, 1999). Although most studies have been of panels of children with asthma or other chronic respiratory conditions, positive associations have also been reported in healthy children (Mukala et al, 1999; Timonen and Pekkanen 1997; Hoek and Brunekreef, 1993, 1994; von Mutius et al, 1995). Von Mutius et al (1995) found the increased risk of upper respiratory symptoms was greatest when concentrations of NO_2, SO_2 and particles were high. Schwartz et al (1994) found a very substantially increased risk in symptoms which has not been found in other studies. Concentrations of NO_2 and PM_{10}, in this study were relatively poorly correlated suggesting a real effect with NO_2. However, the apparent effect of NO_2 ceased to be significant in two pollutant models with PM_{10}. Most studies have failed to find an association between NO_2 and respiratory symptoms. For example, a major study of children in Europe (the PEACE study) found no consistent association between respiratory health (symptoms and PEF) and NO_2 or PM_{10} despite a wide range in the concentrations of these pollutants (Roemer et al, 1999; 1998).

Some of the studies that have failed to find effects for NO_2 have reported effects with other pollutants. For example, Chew et al (1999) found that acute asthma exacerbation among children in Singapore was related to increases in TSP and SO_2. Several studies have found associations between respiratory symptoms in children and ozone, but not NO_2 or particles. For example, Buchdahl et al (1996) who studied childhood wheezy episodes in London and Gilliland et al (2001) who studied school absenteeism due to respiratory illness in Californian children. The ozone effect was greatest in communities with low levels of ambient PM_{10}. In a small study of Californian children with asthma, Delfino et al (2002) found a significant increased risk of asthmatic episodes associated with 1 hour daily maximum PM_{10} concentrations and 8 hour daily maximum NO_2 concentrations. Asthma symptoms were associated with combined O_3 and NO_2 concentrations suggesting a possible interaction. A significant interaction was also found with PM_{10} and NO_2. Outdoor fungal and pollen particles were associated with symptoms but there were no interactions with air pollution. The apparent effects of individual pollutants were smaller in single pollutant models than in models of combined effects.

Table 6.15: Respiratory symptoms - children

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
LA Pasadena Los Angeles, USA African-American children	onset of symptom episodes shortness of breath wheeze cough symptom days shortness of breath wheeze cough	151.4 129.7 1 hour	51.8 42.6		77.8 123.8 8 hour	 1.47 (-0.10-3.25) **1.36** (0.42-2.52) **1.26** (0.0-2.52) 0.84 (-0.10-1.89) **0.84** (0.2-1.57) 0.31 (-0.31-0.94)	 **11.76** (3.53-21.76) **1.23** (0.59-13.53) **14.71** (7.06-22.94) **8.23** (2.35-14.12) **2.35** (1.18-5.88) **5.88** (2.35-9.41)	Ostro et al (2001)
Prague, Czech Republic	prevalence of wheezing in children		nm			16 (-8-42)	na	Pikhart et al (2000)
Taiwan	illness absence in school children	50-60.5	74.3-80.4	45.6-52.7	91.8-92.2	**6.05** (1.65-10.45)	1 (-1-9)	Hwang et al (2000)
UK (?)	asthmatic exacerbation following an upper respiratory infection in children	10.6				**45** (5-120)		Linaker et al (2000)
	cough in pre-school children						na	Mukala et al (2000)
personal exposure children	chest tightness breathlessness on exertion daytime asthma attach night asthma attack							Smith et al (2000)
preschool children personal exposure to NO_2	cough PEF	21.1				about 5 non sig decrease	na	Mukala et al (1999)
European children (PEACE project)								Roemer et al (1999)
Netherlands, children	respiratory symptoms in children with raised IgE upper respiratory lower respiratory	23.7-54.2	26.6-54.3	4.3-22.5		 **5.0** (0.7-9.0) none	 **3.2** (0.7-63) 1.3 (-0.3-3.2)	Boezen et al (1999)

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*			*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*		
	respiratory symptoms in children with low IgE and without bronchial hyperresponsiveness upper respiratory lower respiratory					 3.24 (-2-9.8) 0.75 (-2.5-3.5)	 0.8 (-1.5-5.7) 1.2 (-0.1-2.8)		
Dutch children with chronic respiratory illness	urban lower respiratory symptoms upper respiratory symptoms cough bronchodilator use nonurban lower respiratory symptoms upper respiratory symptoms cough bronchodilator use	47-51 22-33 	29-48 24-35 	6-23 3.6-8.9 		 3 (-2-9) none 0.75 (-1.5-4.25) **6** (1.5-11) **11.25** (3-22.25) 0.5 (-1.25-2.5) 0.75 (-1-2.75) 3 (-6.5-17.5)	 **5.2** (0.7-11.8) 1.1 (-5-30) 0.5 (-0.9-2.2) **11** (3.5-22.8) **6.1** (0.9-13.6) 0.8 (-0.3-2.1) 0.9 (-0.2-2.0) 0.9 (-1.8-4.5)		van der Zee et al (1999)
22 asthmatic children in California	asthma symptoms 1 hour daily maximum 8 hour daily maximum 24 hour mean					 6.16 (-3.08-22.62) 12.9 (-1.32-35)	 8.0 (-2.6-25.5) 5.0 (-6.8-24.7) 3.2 (-10.8-25.4)		Delfino et al 2002
Finland urban children suburban children	respiratory symptoms	 28 14	 18 13	 6 nm		none	none		Timonen and Pekkanen (1997)
Dutch children	respiratory symptoms	127 max 1 hour	30-144	3-104		none	none		Hoek and Brunekreef (1993)
Dutch children	respiratory symptoms cough upper respiratory lower respiratory any respiratory	127	30-144	3-104		none	same day none **2.6** (1.3) 1.2 (2.2) 0.1 (1.0)	weekly average 6.3 (4.3) 6.4 (4.4) 4.3 (6.0) 4.0 (3.7)	Hoek and Brunekreef (1994)
US children	cough lower respiratory	25.3	30	10.9	73.8	**14.2** (2.1-29.4) 10.5 (-1.0-24.7)	**9.3** (2.3-18) 17.7 (6.7-31.7)		Schwartz et al (1994)

Location	*Health endpoint*	*Mean concentrations (µgm^{-3})*				*% increase per increment (95% CI)*			*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 µgm^{-3})*	*PM_{10} (10 µgm^{-3})*		
	symptoms								
school children exposed to summer smog		58	nm	55	2-56 8 hour	not significant			Cuijpers et al (1995)
Dutch children with chronic respiratory symptoms winter air pollution	 asthma attack wheeze woken by symptoms shortness of breath cough runny nose phlegm					no effect	same day 0.04 (0.09) **0.27** (0.10) 0.08 (0.13) none none 0.35 (0.20) 0.19 (0.17)	weekly average 0.23 (0.13) **0.40** (0.14) 0.17 (0.23) 0.04 (0.18) 0.71 (0.45) **1.15** (0.32) 0.33 (0.38)	Roemer et al (1993)
US – indoor air quality infants	upper respiratory lower respiratory wet cough wheeze					0-0.26 (-1.3-2.1) none none 1.6-5.2 (-3.7-28.6)			Samet et al (1993)

6.6.3 Adults

Most recent studies of the effects of NO_2 in adults have considered ambient NO_2 rather than the effects of indoor air quality (Table 6.16) Many studies have been of relatively small size and this has limited their power to detect effects. For example, Neukirch et al (1998) studied a panel of only 40 adult asthmatics. The largest significant effect reported to be associated with NO_2 was the increased use of reliever inhalers by a group of patients with COPD (Harre et al, 1997). Although most panel studies have involved only nonsmokers, the exposure of adults to environmental tobacco smoke is highly variable. Factors such as the smoking habits of other family members and the amount of time spent in public areas such as bars and clubs where high levels of smoke may accumulate are important influences on exposure.

Tarlo et al (2001) studied cold symptoms in adults and children with asthma in Vancouver, Canada. Almost half of all asthma exacerabations were associated with colds and during most of the year (March to November), these cold associated exacerbations were also associated with sulphur dioxide and nitric oxide. Colds were more prevalent in the winter and associated asthmatic exacerbations were also associated with lower temperatures and higher levels of sulphur dioxide, carbon monoxide and NO_x. Van der Zee et al (2000) studied Dutch adults aged 50 to 70 years and found no association between NO_2 and respiratory symptoms although effects were found for other measures of pollutants (particles, SO_2) in symptomatic adults from urban areas. No associations were found between the respiratory health of adults in rural areas and concentrations of the measured air pollutants. Leuenberger et al (2000) found that short term elevations in respiratory symptoms associated with elevated air pollution tended to last longer in more polluted regions, regardless of whether PM_{10} or NO_2 used as an index of pollution. Ring et al (2001) concluded that NO_2 and fine particulate matter seem to enhance allergic disease whereas coarser dust particles do not. Zeghnoun et al (1999) used respiratory drug sales as a potential marker of respiratory illness. They found associations with NO_2 (and other pollutants) but as the relative risk was greater after an eight day lag than after a one day lag, the significance of their findings seems doubtful. Norbak et al (2000) in a study of the effects of indoor air quality found effects on nasal patency associated with higher concentrations of respirable dust, NO_2, formaldehyde and mould, but effects could not be attributed unambiguously to NO_2.

In addition to studies of the effects of NO_2 in ambient or indoor air, there have been a number of studies of symptoms in ice hockey players who are occasionally exposed to very high levels of NO_2 emitted from propane powered ice-resurfacing machines. Rosenlund and Bluhm (1999) found that players exposed to peak levels of NO_2 of up 2358 μgm^{-3} were nearly eight times as likely to have experienced acute respiratory symptoms than a control group of unexposed players. In the exposed group 55.6% reported symptoms and the risk of pulmonary symptoms increased with increased time spent on the ice. There are also a few case study reports of the effects of accidental exposure to highly elevated levels of NO_2. Bauer et al (1998) report the incidence of acute respiratory symptoms following an accidental release of NO_2 from a railroad car and found a clear association both in time and space of symptoms such as headache, burning eyes, sore throat and pulmonary effects. Although concentrations would have been high relative to typical ambient concentrations, both this case report and the ice hockey studies confirm that environmental exposure to high levels of NO_2 without a concurrent elevation in particle levels could cause adverse effects.

Table 6.16: Respiratory symptoms in adults

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
personal exposure adults	cough							Smith et al (2000)
Netherlands, adults	respiratory symptoms airway lability without lability							Boezen et al (1998)
Paris, France, adults with asthma	respiratory symptoms wheeze nocturnal cough shortness of breath	56.9	31.7 BS 34.2 PM_{13}	21.7	nm	 9.8 (-1.8-28.8) 15.2 (-0.4-43.2) **7** (0-162)	 **8.4** (1.2-18.2) BS none **7.4** (0.4-16.6) BS	Neukirch et al (1998)
Dutch nonsmoking adults with asthma	bronchodilator use shortness of breath woken by breathing problems pain on deep inspiration cough/ phlegm nasal symptoms inhaled steroids	21.1	39.7	4.3	80.1	6 (-4-14) **6** (0-12) 14 (-8-40) 6 (-4-17) 6 (-4-16) none none	**4.8** (0-10) **3.4** (0.6-6.8) **4.8** (0.2-10.8) 2.4 (-2.4-8.8) none none none	Hilterman et al (1998)
15 Pollen allergic individuals	irritation of eyes and nose					effects increased by a factor of 1.06 for a doubling of concentration of NO_x	less consistent effects seen with PM_{10}	Riediker et al (2001)
Christchurch, New Zealand, adults with COPD	night time chest symptoms wheeze reliever inhaler use nebuliser use	mean <25 max 35	mean <40 max 200	mean <10 max 30		 25.7 (-26.7-109.9) 18.5 (-118.1-66.7) **43.1** (13.4-81.1) 45.2 (-9.2-129.4)	 **10.8** (2.0-22.3) none none none	Harre et al (1997)

6.6.4 Vulnerable groups

There is very little information about the relative susceptibility of different groups to the effects of NO_2. This is partly because most studies are specifically of children or of adults that have a respiratory health problem such as asthma. Individual studies have not specifically investigated the relative vulnerability of different groups.

Hiltermann et al (1998) found that severity of asthma is not a good indicator of sensitivity to air pollution. Neukirch et al (1998) found that the effects of air pollution were generally greater in asthmatics using medication. There is insufficient information to determine whether the effects of NO_2 on respiratory symptoms are greater in children than in adults, as the study groups are generally not comparable. Boezen et al (1999) found some evidence that of a stronger association between NO_2 and upper respiratory symptoms in children with bronchial hyperresponsiveness and raised levels of IgE than in those without either. The reverse was, however, true for lower respiratory symptoms. The PEACE study failed to demonstrate that groups expected to be particularly sensitive to the effects of air pollution (children with atopy, cough or asthma) were actually more susceptible to effects (Roemer et al, 1999; 1998).

There is very limited evidence, in the form of a Japanese case study (Shimatsu and Obata, 1996), to suggest that smokers are less susceptible to the effects of NO_2 than nonsmokers. Recovery following an industrial accident involving exposure to high concentrations of NO_2 was much more rapid in smokers than in nonsmokers.

The wide variation in the size of effect found in different panel studies may reflect some differences in the susceptibility of groups selected by slightly different criteria as well as the uncertainties imposed by the relatively small number of participants in most studies.

6.6.5 Temporal relationship between air pollution and symptoms (adults and children)

The effects of NO_2 have generally been found to be greatest for same day concentrations or for concentrations up to 2 days previously, although there is relatively little information from which to draw a conclusion. In general the lag between concentrations and effect is similar for both NO_2 and particles (Table 6.17).

Table 6.17: Lag between pollutant concentration and effects for respiratory symptoms

Study	***Health endpoint***	***NO_2***	***PM_{10}***
Neukirch (adults with asthma)	wheeze nocturnal cough shortness of breath	5 6 0-6	5 4 0-6
van der Zee et al (1999) (children with chronic respiratory illness)	lower respiratory symptoms upper respiratory symptoms cough –urban children cough- nonurban children bronchodilator use	0-4 2 2 2 0-4	0-4 0 2 0 0-4
Harre et al (1997) (adults with COPD)	night time chest symptoms wheeze reliever inhaler use nebuliser use	1 1 0 0	1 1 0 0
Ostro et al (2001)	respiratory symptoms in Afroamerican children	0-3	0-3
Hiltermann et al (1998)	respiratory symptoms in asthmatic adults bronchodilator use shortness of breath woken by breathing problems pain on deep inspiration cough and/or phlegm	 0-6 0 0-6 0 0-6	 0-6 0 0 0 -

6.6.6 Independent effects of NO_2 and the interaction between NO_2 and particles

Most studies have failed to find significant associations between respiratory symptoms and either NO_2 or PM_{10}. Where significant effects have been found with NO_2, significant effects have generally also been found with PM_{10}, which suggests that the apparent effects of NO_2 may be attributable to PM_{10}. In many of the studies, however, concentrations of PM_{10} and NO_2 have been relatively poorly correlated ($r<0.6$; Timonen and Pekkanen, 1997; Schwartz et al, 1994; Roemer et al, 1993 and Hoek and Brunekreef, 1993). These studies include some that found significant associations between NO_2 and some measures of respiratory health. The limited case study information described in section 6.6.3 provides some support for the hypothesis that exposure to relatively high concentrations of NO_2 may cause adverse respiratory effects in the absence of elevated particle concentrations.

In addition to the potential confounding effects of particles, respiratory symptoms can also be caused by a wide range of allergens such as fungal spores (Ostro et al 2001).

6.6.7 Overall assessment of relationship between NO_2 and respiratory symptoms

Few studies of the relationship between NO_2 and acute respiratory symptoms have found a significant association. There is a similar paucity of evidence to link particles to acute respiratory symptoms. The magnitude of the increment in respiratory symptoms associated with a 10 μgm^{-3} increase in NO_2 varies substantially between studies. The results of some studies indicate that the increase in symptoms could be as much as 40% in asthmatics whereas most indicate that the increase is about 5% and a number suggest a much smaller effect or no effect at all. A concentration-response function of 5%/10 μgm^{-3} in asthmatics was selected as the best estimate of the potential magnitude of effects. There is no relationship between mean concentrations of NO_2 and concentration-response functions for respiratory symptoms in either adults or children.

It seems likely that any effect that NO_2 has on respiratory health is extremely small in comparison to other influences on respiratory health such as infection and daily temperature. The inconsistent results of the various studies tabulated in Tables 6.14 and 6.15 may partly reflect the difficulty of detecting the small influence of NO_2 against a background of much stronger influences on respiratory health.

6.7 LUNG FUNCTION

6.7.1 Overview

Lung function is a useful objective measure of respiratory health but is influenced by a large number of parameters including temperature, time of day, infection and workplace exposures to airborne contaminants. This is likely to have weakened the power of epidemiological studies to detect small changes in lung function associated with exposure to air pollution. A number of studies have, however, demonstrated an association between short term exposure to nitrogen dioxide and a reduction in lung function (Table 6.18). For example, a small study of asthmatic women found a significant, immediate decline in PEFR (3.4%) following exposure to NO_2 while cooking, and that levels of exposure to NO_2 while cooking over a two week period were also significantly associated with bronchodilator usage. As other pollutants were not measured, effects cannot be attributed solely to NO_2 (Ng et al 2001). Most studies have considered the effects of ambient air pollution rather than personal exposure concentrations, although effects may be more strongly associated with personal exposure.

Table 6.18: Lung function

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Dutch nonsmoking adults with asthma	PEF	21.1	39.7	4.3	80.1	-0.8 (0.9)	-0.44 (0.84)	Hiltermann et al (1998)
Finland urban children suburban children	PEF l/min with asthma cough without asthma with asthma cough without asthma	 28 14	 18 13	 6 nm		l/min -0.548 (0.312) -0.105 (0.266) -0.949 (0.533) -0.321 (0.482)	 **-1.81** (0.643) none **-3.29** (1.35) -0.959 (0.730)	Timonen and Pekkanen (1997)
Switzerland, adults	Decrement in FVC FEV_1 FEF_{25-75} Decrement in FVC FEV_1 FEF_{25-75}	36.6	38.8 TSP		90.3 8 hour	Single pollutant model **0.73** (0.22-1.23) **0.67** (0.13-21) 0.50 (-0.67-1.65) Multipollutant model 0.41 (-0.37-1.18) 0.31 (-0.42-1.03) 0.07 (-1.50-1.61)	Single pollutant model **0.36** (0.06-0.66) **0.46** (0.14-0.78) 0.64 (-0.05-33) Multipollutant model 0.29 ((-0.09-0.67) **0.41** (0-0.82) 0.77 (-0.12-1.66)	Schindler et al (2001)
Netherlands, children	decrement in PEF in children with raised IgE and bronchial hyperresponsiveness	23.7-54.2	26.6-54.3	4.3-22.5		2.5 (-1.45-5)	1.0 (-0.8-3.3)	Boezen et al (1999)
	decrement in PEF in children with low IgE and without bronchial hyperresponsiveness					2.5 (-1-4.5)	0.7 (-0.7-2.3)	
Paris, France, adults with asthma	PEF $lmin^{-1}$ PEF variability %	56.9	31.7 BS 34.2 PM_{13}	21.7	nm	-3.67 0.26	-3.37 0.31	Neukirch et al (1998)
Dutch children with chronic respiratory illness	urban: PEF nonurban: PEF	47-51 22-33	29-48 24-35	6-23 3.6-8.9		*0.25 (4.5.5)* *2.5 (-1.75-7.25)*	**8.3** (2.4-17.0) **8.9** (1.7-20.3)	van der Zee et al (1999)
Christchurch, New Zealand, adults with COPD	PEF	mean <25 max 35	mean <40 max 200	mean <10 max 30	nm	no effect	no effect	Harre et al (1997)
French meta-analysis	FEV_1 and PEF	53	88 TSP	83	124	inconsistent relationship	about 0.15 (TSP)	Zmirou et al (1997)

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*				*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*		*PM_{10} (10 μgm^{-3})*		
Freiburg, Germany asthmatic children longitudinal study	decrements FEV_1%FVC FEV_1 MEF75% MEF50% MEF25%	>40	nm			asthma 4.37 0.10 0.11 0.22 ns 0.29 ns	not asthma 0.49 ns 0.001 ns none none none	not analysed		Moseler et al (1994)
Helsinki, Finland adult asthmatics	morning PEF Lmin-1 afternoon PEF Lmin-1 evening PEF L min-1	25.3	13.5			**-6.4** (2.9) -11.8 (7.0) -14.9 (8.0)		-1.2 (3.1) none -5.2 (3.7)		Penttinen et al (2001)
Dutch children	FVC ml FEV_1 ml PEF ml/s MMEF ml/s	127 max 1 hour	30-144	3-104		none none none none		-7.3 (2.0) -5.5 (1.0) -8.2 (5.0) -7.7 (3.0)		Hoek and Brunekreef (1993)
Austrian? primary school children	FVC FEV_1 MEF	9.8-32.2				1.5 ml for 2 hour mean 3.1 ml for 12 hour mean nonsignificant effect no effect				Frischer et al (1993)
Dutch children	same day decrement FVC ml FEV_1 ml PEF ml/s MMEF ml/s previous day dec FVC ml FEV_1 ml PEF ml/s MMEF ml/s weekly average dec FVC ml FEV_1 ml PEF ml/s MMEF ml/s	127	30-144	3-104		none		 **6.0** (1.1) **5.5** (1.0) 8.2 (5.0) **6.4** (2.3) **7.3** (2.0) **5.4** (2.1) 2.0 (9.4) 2.8 (4.1) **5.7** (1.5) **5.4** (1.4) 4.1 (6.1) **7.7** (3.0)		Hoek and Brunekreef (1994)
Dutch children with chronic respiratory symptoms winter air pollution	PEFam l/min-decrement lag 0 lag 1 weekly average PEFpm l/min	127 max 1 hour	15-110	5-195		no effect		PM_{10} **0.41** (0.15) 0.19 (0.17) 0.57 (0.47)	BS 0.28 (0.16) 0.14 (0.20) 0.79 (0.49)	Roemer et al (1993)

Location	*Health endpoint*	*Mean concentrations (μgm^{-3})*				*% increase per increment (95% CI)*			*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*		
	lag 0 lag 1 weekly average						0.38 (0.27) 0.38 (0.23) 0.91 (0.51)	none 0.19 (0.22) 0.74 (0.61)	
US children – Los Angeles area	decrement in: FVC am – ml FEV_1 am –ml FVC pm – ml FEV_1 pm – ml ΔFVC am-pm –ml ΔFEV_1 am-pm - ml	63	39		68	 2.1 (0.8) 0.6 (0.9) 0.9 (1.1) 1.4 (0.1) 0.6 (0.9) 2.0 (0.1)	PM_5 2.6 (0.9) 1.1 (1.0) 1.3 (1.1) 1.5 (1.0) 1.2 (1.1) 2.3 (1.0)		Linn et al (1996)

6.7.2 Temporal relationship between air pollution and lung function

The limited information available does not show whether the association between NO_2 and PEF is stronger for concentrations on the same day or concentrations on preceeding days (Table 6.19). In individual studies, the lags for NO_2 and PM_{10} are generally the same. Several studies show that morning PEF is more strongly associated with the previous day pollutant levels whereas afternoon or evening PEF is more strongly associated with same day concentrations (eg Parttinen et al, 1998). This would be consistent with the expectation from toxicological and human volunteer experiments that NO_2 would have a fairly immediate effect on respiratory health (see section 6.1).

Table 6.19: lag between pollutant concentrations and effects

Study	***Health endpoint***	***NO_2***	***PM_{10}***
Schindler et al (2001)	lung function parameters in adults	0	0*
Boezen et al (1999)	PEF in children with raised IgE and bronchial hyperresponsiveness PEF in children with neither	0-4 2	0 2
van der Zee et al (1999)	PEF in urban children PEF in children from nonurban areas	2 0-4	0-4 0-4
Neukirch et al (1998)	PEF asthmatic adults PEF variability	5 2	5** 2**
Parttinen et al (2001)	PEF asthmatics	0-4	0-4
Timionen and Pekkanen (1997)	PEF children	2	4
Linn et al (1996)	lung function, children – morning lung function, children - afternoon	1 0	

**TSP; **black smoke*

6.7.3 Evidence for an independent effect of NO_2

A number of studies have been unable to clearly distinguish the effects of NO_2 from those of particles. For example, Penttinen et al (2001) found that the effects of particles on PEFR in adult asthmatics were strongest for ultrafine particles but the effect of ultrafine particles could not be clearly separated from that of other traffic pollutants including NO_2. Concentrations of NO_2 were well correlated with particle number counts but poorly correlated with PM_{10}. Similarly, Schindler et al (2001) were unable to separate the effects of NO_2 on lung function in Swiss adults from those associated with particles.

6.7.4 Conclusions

There is limited evidence to suggest that NO_2 may have a small effect on lung function. The association of morning PEF with the previous day's NO_2 concentrations and of evening PEF with same day concentrations provides circumstantial evidence that the association may be real. The failure of epidemiological studies to consistently detect significant effects may reflect both the small size of the effect and the large number of confounding factors affecting lung function. The significance of the observed changes in lung function associated with NO_2 is unclear. It is suggestive of a small adverse effect on respiratory health, but is difficult to interpret with respect to any kind of quantification of the effects of NO_2.

6.8 RESTRICTED ACTIVITY DAYS

Despite the potential economic importance of restricted activity days arising from ill health caused by air pollution, this health end point has not been widely investigated (Table 6.20). Recently Stieb et al (2002b) have shown nonsignificant associations between concentrations of NO_2 or PM_{10} and restricted activity days. $PM_{2.5}$ was shown to be significantly associated with restricted activity days. The confidence limits for the concentration response functions

are extremely wide indicating a high level of uncertainty about the true magnitude of effects. The contribution of individual pollutants to the overall impact of urban air pollution on health could not be determined. Given the potential importance of this health endpoint, it is included in the quantification using the concentration-response relationship derived by Stieb et al (2002b).

Table 6.20: Other health endpoints

Location	*Health endpoint*	*% increase per increment (95% CI)*			*Study*
		NO_2 (10 µgm^{-3})	*PM_{10} (10 µgm^{-3})*	*$PM_{2.5}$ (5 µgm^{-3})*	
Canada	restricted activity days	5.26 (-24.10-14.10)	14.9 (-5.46-39.59)	16.59 (2.88-32.58)	Stieb et al (2002b)
StrasbourgFrance	myocardial infarction		**0.228** (0.211-0.246)*	none	Eilstein et al (2001)

6.9 CARDIOVASCULAR ILLNESS AND OTHER CIRCULATORY AND BLOOD DISORDERS

A number of studies have investigated the causes of reported relationships between air pollution and increased rates of cardiovascular mortality and hospital admission for cardiovascular causes.

Eilstein et al (2001) report that nitric oxide, NO_2 and ozone were all significantly associated with myocardial infractions in Strasbourg during 1984 and 1989. No association was found for particles (PM_{13}). They suggest that NO_2 may have been a proxy for fine particles.

Schwartz (2001) in a study of blood markers of cardiovascular risk (fibrinogen levels, platelet counts and white blood cell counts) found associations with PM_{10} but not with NO_2. In contrast Pekkanen et al (2000) report that an interquartile increase in concentrations of NO_2 (61 µgm-^{3}) was associated with a 1.5% (0.4-2.5%) increase in fibrinogen concentrations. The association was stronger in the warm season, when associations with PM_{10} and black smoke were also found.

Peters et al (2000) found limited evidence of an association between cardiac arrhythmias and NO_2 concentrations, but the effect is not clearly separable from those associated with carbon monoxide, carbon and fine particles.

There is limited toxicological evidence that exposure to extremely high concentrations of NO_2 may give rise to methemoglobinemia in animals. Groszek et al (1996) found no evidence that ambient NO_x concentrations in Krokow had any effects on blood methemoglobin levels in exposed individuals.

Overall, it is apparent that NO_2 shows apparent associations with several markers of cardiovascular health. There is no conclusive evidence that the apparent effects can be attributed to NO_2 as opposed to some other component of the pollution mix such as fine particles.

6.10 DIARRHOEA

Farrow and Farrow (1999) suggest that exposure to high levels of NO_2 in indoor air may be associated with diarrhoea in infants as a result of the direct action of oxides of nitrogen in the gut. They cite two recent studies that had found such an association in infants including Farrow et al (1997). Farrow et al (1997) studied infants exposed to NO_2 and NO_x found that the only symptom that was significantly associated with indoor levels of NO_2 was diarrhoea, but there was no association between gas cooking and diarrhoea.

This health endpoint has not been widely investigated with respect to exposure to NO_2 or other air pollutants and therefore the significance of the reported association is unclear.

6.11 MECHANISTIC STUDIES

Steerenberg et al (2001) reported that changes in peak expiratory flow, exhaled nitric oxide levels and nasal markers of inflammation in Dutch children were associated with PM_{10}, black smoke, NO_2 and nitric oxide. The response of urban children was greater than for suburban children exposed to the same increment of air pollution. Concentrations of nitrogen dioxide were 1.5 times greater in the urban area and concentrations of black smoke were 2.7 times greater.

A Polish study of men occupationally exposed to NO_2 found raised levels of leukocytes and lymphocytes and an increased number of TCD3+ cells, T CD8+ cells and an enhanced CD4+/TCD8+ ratio (Rutowski et al 1998). The authors concluded that NO_2 may play an important role in the inflammatory process but that exogeneous NO seems to have a modulating effect on the activity of NO_2.

Bernard et al (1998) found limited evidence to suggest that personal exposures to nitrogen dioxide were associated with levels of antioxidants in plasma, specifically carotene in those exposed to more than 40 μgm^{-3} of NO_2.

Overall the results of these studies suggest that exposure to ambient NO_2 may cause low level inflammation and oxidative stress within the lung, providing a causal link between NO_2 and adverse health effects. It is unclear, however, whether observed effects can be attributed unambiguously to NO_2 or whether they reflect exposure to some other unmeasured pollutant such as ultrafine particles. There is limited evidence to suggest that individuals are able to adapt to prolonged exposure to NO_2.

6.12 DISCUSSION

6.12.1 Selection of concentration-response functions for quantification

There is considerable variability in the findings of epidemiological investigations into the effects of air pollution. This partly reflects the difficulty of precisely quantifying what appear to be relatively small effects against high levels of background variability in the health outcomes of interest. It may also reflect marked differences in pollution mix between studies. This may be important, both in terms of the potential interaction between pollutants and also if effects attributed to NO_2 are actually caused by some other component of urban pollution. The relationship between concentrations of NO_2 and those of the confounding pollutant may vary substantially between location. The results of a number of studies suggest that NO_2 is a good marker of traffic pollution and it is possible that effects attributed to NO_2 are actually due to some other component of traffic pollution such as ultrafine particles. This is discussed in more detail below.

Differences in statistical methods, the treatment of confounders and assessment of pollutant concentrations may also contribute to apparent differences in the findings of different studies. Tobias et al (1999) describe how the use of different models, including different confounding variables gives rise to markedly different estimates of the effect of a pollutant on health. There are some major contradictions in the findings of studies performed by different groups at different times with some studies showing health effects to be most strongly associated with particles and a few studies showing that oxidant gases are much more important than particles. It is difficult to judge how important methodological factors may be in giving rise to such markedly different findings.

Table 6.21 summarises the concentration-response functions selected for quantification in Chapter 8. The increase in effects for a given increment in concentrations of NO_2 is generally larger for the less serious health endpoints, which seems plausible. Only a small proportion of GP consultations lead to hospital admissions and only a small proportion of hospital admissions lead to death.

Table 6.21: Summary of concentration-response function for short term effects

Health endpoint	***Concentration-response function %change/µgm^{-3}***
acute mortality	0.05
hospital admission – respiratory	0.07
hospital admission – cardiac	0.07
GP consultations for respiratory illness	0.23
symptom days per person – respiratory symptoms	0.5
days of acute respiratory illness per person	0.5

The absence of a relationship between the slope of concentration-response functions in different studies and mean concentrations of NO_2 is consistent with the change in concentration being more important than absolute concentrations. This is consistent with the toxicological evidence for adaptation but is less consistent with the toxicological evidence for a threshold for effects (section 4.18).

6.12.2 Exposure assessment

The relationship between personal exposure concentrations and concentrations measured at central monitoring points is an issue for all pollutants found in ambient air. It is of particular importance with respect to nitrogen dioxide as personal exposures are heavily influenced by exposure to emissions from gas appliances in the home. Although it can be argued than an increase in outdoor concentrations of NO_2 would result in a population wide increase in mean exposure, this may not actually be the case (Ch 3). It is arguable that the correlation between mean personal exposure concentrations and outdoor levels would be greatest in elderly people as they tend to vary their daily activities less than people of working age or children. They are also more likely to use gas appliances regularly with less regard to outside conditions and/or be catered for. This could explain the stronger association between NO_2 and various health endpoints in older people than found for the general population.

Smoking and environmental tobacco smoke are not normally considered to be an important confounding factor in time series studies because smoking habits remain more less similar in the study population through time. The effect of smoking, however, may contribute to the small size of effects observed in time series studies of NO_2, because the relative influence of fluctuations in the ambient concentration on smokers' personal exposures to NO_2 is so small compared to that for nonsmokers (section 3.6). The health effects on NO_2 are therefore likely to be more clearly distinguished in nonsmokers (see also factors affecting vulnerability, section 6.12.4).

6.12.3 Temporal relationship between ambient concentrations of NO_2 and reported effects

The effects of NO_2 are greatest within the few days immediately following exposure, but the apparent lag between exposure and effects varies between studies. Most studies of daily mortality show strongest association with the previous day's NO_2 concentrations whereas hospital admissions, GP consultations and symptoms are more strongly associated with mean concentrations over several days rather than on a single day and emergency hospital visits are most strongly associated with same day concentrations. There is limited evidence to suggest that lung function early in the day is most strongly associated with the previous day NO_2

whereas that later in the day is most strongly associated with same day concentrations. There was no consistent difference between NO_2 and PM_{10} (or black smoke) in the lag between pollutant concentrations and effect despite an expectation that the effect of NO_2 would be more immediate whereas the effects of particles might be more persistent.

The lack of a consistent lag between NO_2 concentrations and effect may partly reflect the small size of the effect, the small differences in the apparent size of the effect associated with different lags and the poor relationship between ambient concentrations of NO_2 and personal exposure. The studies of daily mortality, emergency hospital visits and lung function provide some evidence that the respiratory effects of NO_2 are fairly immediate as would be expected from the results of experimental studies. The common association of effects with average NO_2 concentrations over several days may imply that the duration as well as the intensity of high pollution events has an important influence on the severity of observed effects. This is less consistent with the experimental results and may imply that NO_2 is not the sole cause of the observed effects.

Epidemiological studies have not been designed to specifically assess the importance of short term (1 hour or less) peaks in concentrations of ambient NO_2 in giving rise to effects.

6.12.4 Factors affecting vulnerability to NO_2

The results of a number of studies have suggested that the association between NO_2 and a range of health endpoints is weakest for adults of working age. Effects on mortality may be slightly increased in the elderly and in those with pre-existing illness. Effects on hospital admissions and primary healthcare usage are increased in both children and the elderly. Effects on emergency hospital treatment for asthma are greatest for children. It is unclear from the available studies whether effects on respiratory symptoms or lung function differ in different age groups. Although it seems plausible that children and the elderly may be the more susceptible to the effects of NO_2 than adults of working age, it is not possible to unambiguously attribute effects to vulnerability because of possible differences in exposure. It is possible that the weaker relationships seen in adults of working age reflects the poorer correlation of personal exposure to NO_2 with ambient concentrations in this age group and/or a greater prevalence of smoking in this age group.

6.12.5 Seasonal effects and other factors modifying the apparent impact of NO_2

There is no consistent evidence to suggest that concentration-response functions for NO_2 differ between the winter and summer. Seasonal differences tend to be small and not significant and could even reflect inadequate control for temperature in the statistical analyses of some studies. It is not possible to judge whether extremes of temperature potentiate the effect of NO_2 from the way study results are presented. In practice, the impacts of ambient NO_2 on the health of individuals in the UK are likely to be slightly higher during the winter than during the summer because mean concentrations of NO_2 are higher (section 3.3).

It is not possible to determine from the available epidemiological studies whether NO_2 potentiates the effect of aeroallergens on the health of susceptible individuals.

6.12.6 Evidence for an effect independent of that of particles

There is a growing consensus that particles are the most important component of air pollution with respect to health. Many investigators have found it difficult to establish the true importance of NO_2 in the relationship between air quality and health because concentrations of NO_2 were correlated with those of PM_{10}. A number of studies have however, demonstrated significant associations between NO_2 and various health endpoints (acute all cause,

respiratory and cardiovascular mortality, emergency hospital admission for cardiovascular illness) even where concentrations of NO_2 were not strongly correlated with PM_{10}.

It has been suggested that NO_2 may simply be a marker for some other component of traffic pollution that has a substantial effect on health such as ultrafine particles. This is difficult to investigate using published epidemiological studies as few have specifically measured ultrafine particles. Pentinnen et al (2001), however, found that lung function was more strongly associated with ultrafine particles than with NO_2, although concentrations of the two pollutants were highly correlated. In principle, emissions of NO_2 and ultrafine particles are likely to be strongly correlated. In studies where the pollution mix was dominated by vehicle emissions with relatively little modification due to photochemical reactions, it would be reasonable to expect that concentrations of NO_2 and ultrafine particles would have been well correlated. This would be typical of most studies undertaken in northern and Western Europe and of wintertime conditions in the USA. In studies where there were high levels of photochemical activity, however, concentrations of NO_2 would have been reduced during the formation of ozone whereas concentrations of fine particles ($PM_{2.5}$ rather than ultrafine) would have been increased by the formation of secondary sulphate and nitrate species. It is questionable whether these secondary soluble species would have a similar toxicity to primary combustion generated particles because of their failure to persist within the lung. Concentrations of NO_2, however, are still likely to be less well correlated with traffic generated ultrafine particles than in the absence of photochemical activity. Photochemical activity is likely to be greatest during the summer months, particularly in North America, southern Europe and south-east Asia. For example, in a North American study, Burnett et al (1997) found a much poorer correlation between concentrations of NO_2 and fine particles than between NO_2 and PM_{10} ($r = 0.45$ as opposed of 0.61). Ozone concentrations might provide a way of separating studies with low levels of secondary pollutant formation from those with higher levels. Unfortunately, the reporting of ozone concentrations is very inconsistent (1 hour, 8 hour or 24 hour mean) and this hampers cross study comparison.

A number of studies have demonstrated significant associations between NO_2 and all cause acute mortality in areas where moderate to high levels of summertime photochemical activity are likely (Saez et al, 2002; Kwon et al, 2001; Mar et al, 2000; Simpson et al 2000; Ostro et al, 2000; Loomis et al, 1999; Ostro et al, 1999). Only one of the studies reviewed demonstrated a significant association between NO_2 and respiratory mortality where high levels of photochemical activity were likely (Simpson et al, 2000). Similarly only one of the studies showed a significant association for cardiovascular mortality (Mar et al, 2000). For hospital admissions, Linn et al (2000) found significant associations between NO_2 and admissions for pulmonary, cardiovascular and cerebrovascular admissions under conditions where moderate to high levels of photochemical activity were likely. Sunyer et al (1998) found a significant association between NO_2 and admissions for asthma that was probably associated with moderately high levels of photochemical activity. Braga et al (2001) and Castellague et al (1995) found significant associations between NO_2 and emergency hospital visits for asthma that were similarly associated with probable elevated levels of photochemical pollution. Norris et al (1999), however, did not find an association between emergency visits for asthma and NO_2, but did find an association with $PM_{2.5}$. The results of studies of respiratory symptoms are very inconsistent, but a number of studies have demonstrated significant associations between NO_2 and respiratory health under conditions where concentrations of photochemical pollutants are likely to have been elevated (Ostro et al, 2001; Hwang et al, 2000; Hiltermann et al, 1998).

Overall the evidence suggests that NO_2 is associated with adverse effects on health, even under conditions where concentrations of NO_2 and traffic generated ultrafine particles are unlikely to have been well correlated. Although some of the apparent effects of NO_2 may be due to exposure to ultrafine particles, it seems unlikely that confounding by ultrafine particles would account for all the apparent effects of NO_2.

6.12.7 Evidence that NO_2 potentiates the effects of particles

The results of the APHEA 2 study suggest that the effects of PM_{10} on daily mortality may be enhanced at high concentrations of NO_2 (Katsouyani et al, 2001), but this finding is not borne out by the findings of other studies of daily mortality from all or cardiovascular causes. There is very limited evidence that the effects of PM_{10} on respiratory mortality rates may be enhanced in areas with high concentrations of NO_2. In addition, Spix et al (1998) reported that the effects of black smoke on respiratory hospital admissions were greater on days when concentrations of NO_2 were elevated. Investigation of the relationships between the concentration-response function for PM_{10} and mean concentrations of NO_2 for other studies of hospital admission and other health endpoints did not, however, reveal a general relationship between the slope of the concentration-response functions for PM_{10} and concentrations of NO_2. An alternative explanation for the APHEA 2 results would be that NO_2 was merely a marker for ultrafine particles in traffic pollution and that increased NO_2 concentrations were coupled with an increased proportion of ultrafine particles in PM_{10}. Given that ultrafine particles may be more toxic per unit mass than PM_{10} (EPAQS, 2001), an increased proportion of ultrafine particles in PM_{10} would be expected to give rise to a steeper concentration-response function. There is some uncertainty in this explanation for the apparent effects of NO_2 on concentration-response functions for PM_{10}, as ultrafine particles would be expected to affect cardiovascular health as well as respiratory health. The absence of a general relationship between NO_2 levels and the steepness of concentration-response functions for PM_{10} may reflect the importance of photochemistry in modifying concentrations of NO_2 and fine particulate.

In summary, there is limited evidence to suggest that NO_2 may potentiate the effects of PM_{10} with respect to serious respiratory illness, but this could be an artefact of the strong correlation between concentrations of NO_2 and ultrafine particles in some cities.

6.12.8 Evidence that NO_2 affects cardiovascular health

The results of animal toxicology and human volunteer studies suggest that an association between NO_2 and respiratory health may be plausible, although effects have only been observed at relatively high concentrations of NO_2 (Chapters 4 and 5). The mechanisms by which NO_2 could affect cardiovascular health are less clear, although there is limited experimental evidence that links NO_2 with an increased risk of narrowing of the atherosclerosis (coating of the arteries; section 4.11).

The results of epidemiological studies suggest that the effects of NO_2 on deaths from respiratory causes or hospital admissions for respiratory illness are little different from those observed for cardiovascular disease. There is much better mechanistic evidence to link cardiovascular illness with ultrafine particles (Schwartz 2001, Donaldson et al, 2001) and Anthony Seaton believes that the apparent link between NO_2 and cardiovascular health events is entirely due to the confounding effects of ultrafine particles (personal communication, 2003). The cardiovascular effects of ultrafine particles are attributed to the release of inflammatory mediators into the blood stream rather than the direct action of the particles (Donaldson et al, 2001). The effects of NO_2 on cardiovascular parameters have been much less extensively studied than those of particles. There is a possibility that NO_2 does make a small contribution to cardiovascular illness through its contribution to pulmonary inflammation. Current thinking is that any effect of NO_2 on cardiovascular health is likely to be much smaller than that of ultrafine particles.

6.13 CONCLUSIONS

The results of the numerous epidemiological investigations of the short term effects of exposure to NO_2 are inconsistent and there is considerable uncertainty about the relationship

between personal exposure concentrations of NO_2 and the measurements used in epidemiological analyses. The health endpoints for which there is the most consistent evidence of a relationship with NO_2 include daily mortality, emergency hospital visits for asthma and use of primary health care facilities.

The apparent health effects of NO_2 often disappear in multipollutant models that include particles and/or ozone. NO_2 is strongly associated with traffic pollution and it is possible that effects attributed to NO_2 are actually due to some other component of traffic pollution such as fine particles. Significant associations have been found between NO_2 and various health endpoints, however, even in the absence of a strong correlation between concentrations of NO_2 and fine particles.

Overall, the evidence points towards a small independent role for NO_2 in the association between air quality and health that is separate from that associated with fine particles. Uncertainties in exposure estimation and the strong correlations that exist between concentrations of different pollutants have tended to obscure the influence of NO_2 on health. The inconsistency of the results of epidemiological studies would be consistent with the role of NO_2 being much less important than either particles or ozone, in the association between air quality and health.

7. EPIDEMIOLOGICAL STUDIES: LONG TERM EFFECTS

7.1 INTRODUCTION

This chapter describes the results of epidemiological studies of the long term effects of exposure to NO_2. The health endpoints considered are mortality, respiratory illness, asthma, cancer, lung function and effects on the unborn child. An assessment is made of the strength of evidence for an association between NO_2 and each health endpoint, the extent to which the apparent effects of NO_2 may be due to an unmeasured co-pollutant and the size of effects that may be attributed to NO_2. There is relatively little information about the effects of ambient NO_2 on health and therefore studies of indoor air have also been reviewed. Given that most of the information about NO_2 in indoor air has been inferred from studies of children's respiratory health in relation to gas cooking, there is considerable uncertainty about the attribution of effects to NO_2. The pollutant mix in indoor and outdoor air is different and the apparent effects of NO_2 in indoor and outdoor air, may not necessarily be comparable.

7.2 MORALITY

There is a well established link between exposure to airborne particles and premature mortality (eg Abbey et al, 1999; Dockery et al, 1993; Pope et al, 1993, 2002). Early estimates of the scale of the effect suggested that lifetime exposure to 25 μgm^{-3} of PM_{10} was associated with a loss of life expectancy of about a year (COMEAP, 1998). More recent studies have suggested a somewhat smaller effect.

There is relatively little information about the effects of NO_2 on life expectancy (Table 7.1). Abbey et al (1999) found a nonsignificant association between all cause, cardiopulmonary and lung cancer mortality in males and cardiopulmonary mortality in females and NO_2. A significant association was found between lung cancer in females and NO_2. In a re-analysis of the Harvard Six Cities study (Dockery et al, 1993), Krewski et al (2000) found significant associations between NO_2 and mortality from all and cardiopulmonary causes. Concentrations of NO_2 were, however, strongly correlated with those of particles, such that it was impossible to separate the effects of NO_2 from those of particles. Less than 10 000 adults were included in the study and the exposure categories were limited by the limited number of cities. In a re-analysis of the American Cancer Society study in which 1.2 million adults were enrolled (Pope et al, 1993), Krewski et al (2000) failed to find associations between NO_2 and all cause, cardiopulmonary, lung cancer or respiratory mortality. These health endpoints were, however, significantly associated with fine particles ($PM_{2.5}$) and sulphate and sulphur dioxide. Concentrations of NO_2 and particles were less strongly correlated than in the Six Cities study and much greater variability in concentrations of each pollutant was present, such that it was possible to distinguish the effects (or absence of effects) of NO_2 from those of particles. Bobak et al (1999) showed a significant association between NO_2 and infant mortality, but there was a stronger relationship with TSP. Hoek et al (2002) did not find a significant association between NO_2 and mortality when regional levels of NO_2 were considered. They did, however, find a significant association when exposure estimates were revised to include the extra contribution of NO_2 from local traffic. This suggests that the effects of NO_2 may be obscured in some epidemiological studies of large populations because of inadequate exposure estimation.

Overall, there is no evidence that long term exposure to ambient levels of NO_2 has a substantial effect on life expectancy. The results of the American Cancer Society study strongly suggest that NO_2 has no effect but further studies are required for corroboration. The effects, if any, of ambient nitrogen dioxide on life expectancy appear to be much smaller than those associated with ambient particles.

Table 7.1: Mortality associated with long term exposure to NO_2

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
California, 7th Day Adventists: male	all cause					0.8 (-2.8-4.52)	4.6 (-0.8-10.8)	Abbey et al (1999)
	cardiopulmonary					0.26 (-3.72-5.04)	4.2 (-2.5-12.5)	
	nonmalignant respiratory					none	9.6 (-2.5-25.3)	
	lung cancer					21.6 (-1.86-0.7)	**93.8** (23.7-257)	
female	all cause					none	none	
	cardiopulmonary					0.8 (-2.72-4.78)	none	
	nonmalignant respiratory					none	4.2 (-1.7-16.6)	
	lung cancer					**48** (3.98-156.24)	13.7 (-16.6-81.0)	
Re-analysis of Harvard 6 Cities Study		11.6-41.7	18.2-46.5				$PM_{2.5}$	Krewski et al (2000)
	all cause					8.3 (2.3-15.3)	15.1 (4.8-21.5)	
	cardiopulmonary					9.3 (1.3-19.6)	17.2 (3.8-33.9)	
	lung cancer					5.0 (-11.6-34.5)	9.1 (-17.7-55.9)	
Re-analysis of ACS Study			fine particle 18.2 (9.0-33.5)				fine particles	
	all cause					none	11.0 (7.3-15.1)	
	cardiopulmonary					none	16.7 (11.0-22.9)	
	cardiovascular					none	19.2 (13.1-26.6)	
	respiratory					none	2.8 (-8.2-17.1)	
	lung cancer					none	9.4 (-1.6-23.3)	
Netherlands	ambient air pollution	36		17			BS	Hoek et al (2002)
	cardiopulmonary					18 (-9.7-64)	34 (-32-164)	
	all cause					12.3 (-1-31.3)	37 (-5-97)	
	ambient and local pollution					27 (-0.7-78)	**71** (10-167)	
	cardiopulmonary					**15** (1.7-37)	**37** (6-77)	
	all cause							

7.3 RESPIRATORY EFFECTS

7.3.1 Overview

This section discusses the outcome of the WHO (1997) review of the respiratory effects of nitrogen dioxide and the results of more recent studies. Studies of the effects of ambient NO_2 and NO_2 in indoor air are discussed separately. The WHO (1997) only reviewed studies of children and most of the other studies available have investigated effects in children rather than adults. The WHO also discussed only lower respiratory symptoms and most other investigators have similarly focussed on lower respiratory symptoms.

7.3.2 The WHO review: indoor air

The WHO (1997) reviewed the association between respiratory illness in school age children and indoor concentrations of NO_2. Of a total of 22 studies available for indoor air, only 9 were selected for inclusion in a combined analysis. These studies were selected on the basis that the health endpoint investigated was reasonably close to a standard definition of lower respiratory symptoms, that there was some estimate of exposure and the odds ratio was either calculated, or the published information allowed calculation of the odds ratio. Eight of the selected studies were cross sectional in design. In five of the studies, the exposure differential was the presence/absence of gas cooking and gas cooking was assigned a concentration increment of 29 ug^{-3}. Only two of the nine studies corrected for parental smoking. The odds ratio across all 9 studies for an increase in NO_2 concentrations of 29 μgm^{-3} was 1.17 (1.11-1.23) in a fixed effects model and 1.18 (1.09-1.27) in a random effects model. The UK studies included in the analysis gave a slightly higher odds ratio than the US studies. Although the WHO (1997) comments that these results are robust, what they actually show is an association between gas cooking and lower respiratory symptoms, rather than necessarily an association with NO_2. Even if oxidised nitrogen compounds did play an important role in the association with respiratory effects, it is possible that the causal agent was nitrous acid rather than NO_2. A higher odds ratio was found where NO_2 was measured rather than inferred from the presence or absence of gas cooking, but the confidence interval was also greater, although this could reflect the smaller number of studies. The higher odds ratio would be consistent with the effects not being specific to NO_2, although NO_2 may be a reasonable measure of exposure with respect to the pollutant mix that was giving rise to effects. Most of the studies excluded from the WHO analysis had not found effects, although the endpoints examined were generally not specifically lower respiratory symptoms. The findings of studies of the relationship between NO_2 and the prevalence of wheeze, asthma, cough and absence from school because of respiratory illness, have been contradictory (WHO, 1997).

The WHO (1997) reviewed respiratory effects in very young children (those under 2 years) separately from older children. Only seven studies of the effects of NO_2 in indoor air were available for analysis and only one of these studies showed NO_2 to have a significant impact (hospitalisation for chest illness). The results of 5 of the 7 studies were suggestive of an association between NO_2 and respiratory health, although exposure levels were generally inferred from the presence/absence of a gas cooker, so that effects were not specific to NO_2. The WHO (1997) concluded that the evidence was not strong enough to suggest an effect in young children comparable to that seen in older children.

Overall, the evidence presented by WHO would be consistent with a possible association between gas cooking and lower respiratory symptoms in children, but is not strongly supportive of an association between indoor concentrations of NO_2 and respiratory symptoms. There is an inconsistency between the absence of effects in young children who spent much more time in the home environment than school age children and the inferred presence of effects in school age children.

7.3.3 The WHO review: outdoor air

The WHO (1997) identified 3 main studies (Table 7.2). The Harvard Six Cities study found nonsignificant associations between NO_2 and various respiratory symptoms (bronchitis, chronic cough and chest illness), but stronger effects were associated with TSP. The 95% confidence limits for the odds ratio with NO_2 were extremely wide. No association was found between wheeze or asthma and NO_2. Braun Fahrlander et al (1992) found an association between the duration of respiratory episodes in Swiss children and NO_2, but no association between the incidence of respiratory illness and annual mean concentrations of NO_2. Jaakola et al (1991) found that the frequency of upper respiratory infections in 6 year old children was significantly associated with NO_2, but a relationship was not found for children aged 14 to 18 months.

Overall the studies reviewed by WHO (1997) provide evidence of a possible weak relationship between respiratory health and NO_2 but it is difficult to attribute effects to NO_2 rather than air pollution more generally. The absence of effects in several studies suggest that the effects of NO_2 on health are likely to be relatively small.

7.3.4 Other studies: indoor air

A meta-analysis of 14 studies of children's health undertaken by Li et al (1994) found a significant increased risk of respiratory illness other than asthma associated with indoor concentrations of NO_2 in children of 5 to 12 years in age in both the US and Europe. Nonsignificant increased risks of respiratory illness were found in children under 5 years in age. All of the studies considered in the meta analysis reported by WHO were included together with a further 5 studies. The study was not specific to lower respiratory effects and where a range of health endpoints was given in individual studies, the authors selected the endpoint that was most representative of the study findings rather than closest to a common endpoint. In common with the WHO analysis, the increment in NO_2 exposure associated with gas cooking was assumed to be 30 μgm^{-3}. In a fixed effects model, the odds ratio for children's respiratory illness with an increase of 30 μgm^{-3} of NO_2 for US children aged 5-12 was 1.30 (95% CI 1.12-2.03). That for European children was 1.35 (1.21-1.51). The corresponding odds ratios for infants were 1.25 (0.92-1.70) and 1.30 (1.00-1.69). The odds ratios for children aged 5 to 6 were slightly greater than those for children aged 5-12. In a random effects model, the odds ratios were generally similar to those derived in the fixed effects models, but the confidence intervals were wider.

There is relatively little more recent information about the effects of NO_2 in indoor air. A series of studies of Australian children have found inconsistent effects. Garret et al (1998) found that NO_2 was a marginal risk factor for respiratory symptoms and that there was an association between respiratory symptoms and gas cooking, even after controlling for NO_2 exposure. Atopic children tended to have a greater risk of respiratory symptoms than nonatopic children on exposure to gas cooking fumes or NO_2. Ponsonby et al (2001) found no association between NO_2 exposure or gas heater use and asthma or wheeze. There was a nonsignificant association with gas cooking. Ciuk et al (2001) in a study of preschool children reported an association between indoor concentrations of nitrogen dioxide and respiratory symptoms but did not provide details. No association was found between exposure to NO_2 and urinary nitrate.

The results of studies undertaken elsewhere are similarly inconsistent. Pershagen et al (1995) found that gas cooking was a risk factor for the development of wheezing bronchitis in girls but not boys. Pikhart et al (1997) found an association between school levels of NO_2 and the prevalence of wheeze (lifetime and last 12 months) in Czech children, however home levels of NO_2 were negatively associated with symptoms. It seems unlikely that personal exposure concentrations would be more strongly correlated with indoor concentrations of NO_2 at school

than at home, so the relevance of this finding is unclear. Particle concentrations were not measured. Shima and Adachi (2000) found an association between indoor concentrations of NO_2 and respiratory symptoms (bronchitis, wheeze and asthmatic symptoms) in girls but not boys The magnitude of the effects seem implausibly large and are associated with extremely wide confidence intervals (Table 7.2). Particle concentrations were not considered so that effects are not unambiguously associated with NO_2.

A few studies of sick building syndrome have highlighted the potential importance of NO_2 in workplace air, although the syndrome has been more commonly associated with poor ventilation and high levels of carbon dioxide. Menzies et al (1996) found that eye symptoms in office workers were associated with high concentrations of dust and NO_2. Mucosal symptoms were associated with total volatile organic compounds, NO_2 and total contaminant load. Systemic symptoms were associated with dust.

7.3.5 Other studies: outdoor air

Studies in which both NO_2 and particles were measured

Only a few of the more recent studies of the effects of NO_2 in ambient air have considered both NO_2 and particles (Table 7.2). McConnell et al (1999) found associations between NO_2 and phlegm and between PM_{10} and bronchitis in children with asthma but not in other children. Although the association between NO_2 and phlegm was strongest, relationships also existed with particles such that an independent effect was not established. Concentrations of NO_2 and PM_{10} were well correlated. In contrast with the results of many studies, there was no association of respiratory symptoms with ozone. Braun Fahrlander et al (1997) found associations between NO_2 and various measures of cough and bronchitis but effects were also found with PM_{10} and concentrations of the two pollutants were strongly correlated. The association between respiratory symptoms and NO_2 (or particles) was stronger in children with a family history of asthma and allergies, although the difference between these children and other children was not statistically significant. A German study of asthmatic children, found an association between symptoms and exposure to NO_2, but not O_3, NO, SO_2 or particles (Seidler et al, 1996). Linn et al (1996) found that the prevalence of a wide range of respiratory symptoms in children was greater in communities with poorer air quality, but the effect was not significant nor was it specific to NO_2.

Zemp et al (1999) found an association between NO_2 and respiratory symptoms (breathlessness, chronic phlegm, chronic phlegm or cough) in Swiss adults but concentrations of PM_{10} and NO_2 were highly correlated. The authors were unable to separate the effects of NO_2 from those of particles. A Japanese study found a negative correlation between NO_2 and phlegm and no significant association with other measures of respiratory health, although significant effects were found with O_3 and SO_2 (Setiani, 1996). Jammes et al (1998) found increased symptoms of asthma, but not rhinitis associated with NO_2 and particles in French adults, but were unable to determine the separate effects of the two pollutants.

Overall, these studies do not clearly demonstrate that NO_2 has an effect on the respiratory health of children or adults that is separate from that of particles.

Table 7.2: Respiratory illnesses associated with long term exposure to NO_2 (prevalence of respiratory illness, unless otherwise stated)

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Taiwan, middle school children	asthma prevalence							Guo et al (1999)
Taiwan, adolescents	prevalence of asthma	53	91	34.5	44	Prevalence of asthma 15% greater (10-20%) in children exposed to concentrations >53 μgm^{-3} than those exposed to less than 53 μgm^{-3}	no effect	Wang et al (1999)
Southern California children check	wheeze (boys) wheeze (girls) ever asthma current asthma bronchitis cough	41	34.9		64	**9.87** (0.84-22.9) none 4.4 (-3.2-14.9) none 2.94 (-1.3-8.2) 2.5 (-2.9-9.4)	10.4 (-1.6-26.4) 0.8 (-14.8-26) none none none 13.2 (-2-348)	Peters et al (1999a)
Switzerland	chronic cough chronic phlegm cough/ phlegm wheezing without cold breathlessness – day breathlessness –night breathlessness current asthma dyspnoea on exertion chest tightness	35.6	21.2	11.7	43.1	7 (-4.3-19.6) **14** (3.7-25.3) **11** (2.6-20.1) 1.6 (-7.6-11.5) **18.7** (8.4-29.9) 6.1 (-3.0-16.2) **12.8** (4.8-21.4) none **8.5** (3.2-14.1) none	11.7 (-11.9-41.5) **35.2** (11.0-64.7) **27.4** (7.9-50.5) none **47.2** (22.4-77.2) 10.8 (-8.4-34.0) **32.8** (13.9-54.8) none 31.6 (18.2-46.4) none	Zemp et al (1999)
Southern California Children with asthma Children with wheeze (no asthma) Children with no wheeze or asthma	 bronchitis phlegm cough bronchitis phlegm cough bronchitis phlegm cough					 6.4 (-4.38-26.26) **37.2** (8.74-94.1) 13.14 (-2.18-37.2) none none 6.56 (-6.56-26.26) none none none	 **21.1** (5.3-42.1) **57.9** (21.0-121.0) 5.3 (-10.5-36.8) none none 10.5 (-5.3-42.1) none none none	McConnell et al (1999)
Australian school	cough with phlegm	12-132				0.4		Pilotto et al (1997)

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 µgm^{-3})*	*PM_{10} (10 µgm^{-3})*	
children – indoor concentrations of NO_2 during winter	colds school absence (at least one day)					1.46 4.28		
Austrian children, traffic pollution					nm			Studnicka et al (1997)
Swiss children	chronic cough nocturnal dry cough bronchitis wheeze asthma allergic illness	16-50	10-33	2-33	17-75	**15.3** (3.7-31.0) **26.0** (13.4-4.42) 9.2(-0.3-22.4) none none none	**90** (30-209) **82** (30-169) **51** (9-125) none none none	Braun Fahrlander et al (1997)
US children (Harvard 6 cities study)	Respiratory symptoms Bronchitis Chronic cough Chest illness Wheeze Asthma					 22.6 (-16.1-145.2) 19.4 (-25.8-306.5) 6.5 (-22.6-122.6) none none		Dockery et al (1989)
	Duration of respiratory episodes Incidence of respiratory illness					6.5 (3.5-8) none		Braun Fahrlander et al (1992)
Japanese school children – boys girls	history of allergic illness bronchitis ever wheeze 4th grade 5th grade 6th grade asthma 4th grade 5th grade 6th grade history of allergic illness bronchitis ever wheeze	outdoor 13.3-59.6 indoor 29.1-143.1				outdoor NO_2 none 7.2 (-10.5-33) 8.3 (-14.3-43.5) 15.4 (-9.4-59.4) 25.3 (-7.7-93.0) 6.0 (-17.0-48.95) 22.6 (-7.2-79.8) 14.8 (-15.4-79.8) none 14.8 (-6.0-45.6)	indoor NO_2 2.8 (-8.2-15.4) none none none none none none none **5.5** (6.0-19.2) **23.1** (3.3-49.5)	Shima and Adachi (2000)

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
	4th grade 5th grade 6th grade asthma 4th grade 5th grade 6th grade					17.6 (-10.4-68.8) 8.25 (-17.6-66.0) none 7.7 (-19.2-60.0) **7.7** (3.3-91.3) none	**49.5** (16.5-100.6) **33.0** (3.3-79.2) 12.6 (-12.1-50.6) **34.6** (3.3-84.7) **36.8** (3.3-91.3) none	
US children – infants 5-12 years European children – infants 5-12 years		indoor NO_2				 8.3 (-2.7-23.3) 10 (4.3-18.7) 10 (0-23) 11.7 (7-17)		Li et al (1994)
Swedish pre-school children	wheezing bronchitis girls boys					 about 50 none	not analysed	Pershagen et al (1995)

Studies in which NO_2 but not particles measured

Several studies have investigated the effects of NO_2 in children without consideration of particles. Ramadour et al (2000) found no consistent association between mean levels of NO_2 and the prevalence of rhinitis, asthma or asthmatic symptoms in school children. An association was found between asthmatic symptoms and mean O_3 concentration. Mukali et al (1995) found that children of pre-school age living in central Helsinki experienced more days of stuffed nose and cough than suburban children (26% versus 20% and 18% versus 15% respectively). The difference in NO_2 personal concentrations was 9.2 μgm^{-3} and there was a nonsignificant correlation between NO_2 and cough, although effects were unlikely to have been specific to NO_2. Pilotto et al (1997) found a relationship between school absences for colds and NO_2. A Slovakian study (English abstract cited by Medline) found a higher incidence of serious respiratory disease in children in an urban area with higher concentrations of NO_2 than in an area with lower NO_2 but it is possible that socioeconomic confounding was not adequately allowed for. Shima and Adachi (2000) found that bronchitis, wheeze and asthmatic symptoms were nonsignificantly associated with outdoor concentrations of NO_2 in both girls and boys. Pershagen et al (1995) found an association between the development of wheezing bronchitis in girls of pre-school age and estimated levels of outdoor NO_2. Similar effects were not found in boys, although the incidence of wheezing was greater in boys. The significance of the effects in girls was therefore unclear. Magnus et al (1998) found little evidence of an association between NO_2 and bronchial obstruction in Norwegian children of less than two years in age. Concentrations of NO_2 were generally less than 30 μgm^{-3}.

Forsberg et al (1997) studied Swedish adults living in the vicinity of air pollution monitoring stations in Swedish towns. They found NO_2 was associated with cough and also irritation of the nose and throat. The relationships were stronger in women and in the subpopulation who did not leave the vicinity of the monitor to go to work or school. This would be consistent with the better estimation of exposure for these individuals. Relationships were also found with black smoke so it is not possible to unambiguously attribute effects to NO_2, although concentrations of the two pollutants were only moderately correlated with each other ($r = 0.55$).

Overall, these studies are suggestive of a weak association between NO_2 and respiratory symptoms, but do not provide clear evidence of a relationship. Apparent effects may be due entirely to concurrent exposure to particles.

Studies of traffic pollution

Traffic is a major source of NO_2 and a number of investigators have investigated the effects of traffic pollution on children's health. Hirsch et al (1999), for example, found that the prevalence of cough and bronchitis in German children was associated with traffic pollution, but effects were not specific to NO_2. De Kok et al (1996) found that the prevalence of respiratory symptoms (chronic cough, shortness of breath, wheeze and asthma) in Dutch children was associated with living in areas with different levels of air pollution and highlight NO_2 as a key pollutant. No concentration information was presented however, so effects may not have been specific to NO_2. Similarly, Osterlee et al (1996) found that there was a higher prevalence of respiratory symptoms in children living along busy streets than in children living along quiet roads, even after adjusting for potential confounders. A Dutch study found that lung function and symptoms in children were associated with the density of heavy goods vehicle traffic rather than with NO_2 or passenger car traffic (de Hartog et al, 1997). Nicolai (1999) in a review of respiratory disease in children concluded that there was a significant association between traffic pollution and respiratory symptoms in children.

Several investigators have used NO_2 as a marker of traffic pollution. An Austrian study (Studnicka et al, 1997), for example, found increased odds of wheeze and cough (without cold) were found in communities with elevated levels of NO_2, but there was not a clear dose response relationship.

Overall, there seems to be an association between traffic pollution and respiratory symptoms but the association is not specific to NO_2.

7.3.6 Conclusions

The results of a number of studies are suggestive of a weak association between NO_2 and respiratory symptoms in children and possibly adults, but most studies have failed to find significant effects. Inconsistencies in gender differences in apparent sensitivity to nitrogen dioxide suggest that some of the reported findings have arisen by chance rather than as a result of exposure to NO_2. In many of the studies where apparent effects on respiratory health have been reported, the assessment of exposure to NO_2 has been through estimation rather than measurement. It is possible that observed effects arise through exposure to co-pollutants including nitrous acid rather than necessarily as a consequence of exposure to NO_2. There is a general difficulty in separating the effects of NO_2 on respiratory symptoms from those of particles. In many studies where NO_2 and particles have both been measured, it is impossible to clearly attribute effects to NO_2 rather than concurrent exposure to particles. In the many studies in which particle concentrations were not measured, it is impossible to be certain that effects attributed to NO_2 were not actually caused by concurrent particle exposure.

7.4 ASTHMA AND ALLERGIC DISEASE

The results of several studies have suggested a possible association between exposure to traffic pollutants including NO_2 and the development of asthma (Table 7.2). Guo et al (1999), for example, report that the prevalence of asthma in children was associated with traffic-related air pollution, particularly NO_2 and carbon monoxide. Studnicka et al (1997) found an association between NO_2 (used as a proxy for traffic pollution) and the prevalence of asthma in Austrian children. Wang et al (1999) found an association between asthma in adolescents and NO_2 but not with PM_{10}. Risks were also increased in males and with age, exposure to ETS, smoking, alcohol consumption, higher levels of parental education and place of residence. Nicolai and von Mutius (1997) found substantial differences in asthma prevalence in children between West German towns with high levels of traffic pollution (fine particulate and NO_x) and East German towns with high levels of industrial pollution (sulphur dioxide and smoke). However, when atopy was taken into account, there was not a significant difference in asthma between West and East Germany. Kramer et al (2000) found that atopy and allergy in children was related to outdoor NO_2 concentrations but not to personal exposure concentrations. Outdoor concentrations of NO_2 were related to traffic pollutants so the effects may have been caused by some other component of traffic pollution, rather than NO_2 itself. Jammes et al (1998) found that the prevalence of asthma was greater in French adults exposed to higher levels of NO_2 and particles. The study, however, involved a comparison of adults living in a city centre with those living in a suburban area, so that other confounding factors may have influenced asthma prevalence.

The results of a few studies have suggested an association between asthma and indoor air quality. A Canadian study found that children exposed to levels of NO_2 greater than 19 μgm^{-3} in a short term survey were more likely to have asthma than children exposed to lower levels of NO_2. Asthma was, however, associated with a wide range of other influences on indoor air quality including gas cooking, electric heating, wall to wall carpeting and urea formaldehyde foam insulation.

The majority of studies have found no association between NO_2 and the development of asthma. Oyama et al (1998), for example, found no difference in the rate of asthma and other allergic disease in Japanese children in areas with very different concentrations of NO_2 and other air pollutants. Risks appeared to be slightly related to population density. Vacek et al (1999) found no correlation between asthma prevalence and levels of common air pollutants in a study comparing young people in Canada to those in the Czech Republic. Nicolai (1999) found no correlation between traffic flow and asthma in children. Lunttmann et al (1995) found no association of the prevalence of respiratory and asthmatic illness to exposure due to automobile exhaust as assessed from traffic density, NO_2 and soot. McDonnell et al (1999) found no association between the incidence of asthma in a population of nonsmoking adults in California and exposure to NO_2, although new cases of asthma in men were associated with exposure to O_3. The French PAARC study found an association between the prevalence of asthma in adults (but not children) with sulphur dioxide but not with NO_2 (Baldi et al, 1999). Miyamoto (1997) found no consistent relationship between ambient concentrations of NO_2 and the prevalence of asthma. Asthma in adults was more severe in those living in areas with concentrations of less than 57 μgm^{-3} and asthma in children was more severe in those living in areas with concentrations greater than 57 μgm^{-3}. Asthmatics in urban areas tended to have had an earlier age of onset and were more likely to have had a history of respiratory infection than those from more rural areas.

Most studies have similarly found no association has been found between exposure to NO_2 and the development of allergic disease. Moran et al (1999), for example, in a study of young British adults found no association between childhood exposure to NO_2 as assessed from the presence of a gas cooker in the home and asthma/wheeze, allergic sensitisation or current severity of respiratory symptoms. Charpin et al (1999) found no association between gaseous air pollutants including NO_2 and atopy in a cross section study of French primary school children. Hirsch et al (1999) found no association between atopy and traffic pollution including NO_2 in German children.

Overall there is no consistent evidence that exposure to NO_2 is associated with the development of asthma.

7.5 LUNG FUNCTION

Lung function is affected by a large number of variables and varies daily and throughout each day in response to temperature, air pollution and other factors. It is therefore relatively difficult to detect the long term effects of air pollution on lung function against this background of daily and hourly variability. Most of the relevant studies of lung function have involved children rather than adults (Table 7.3).

The WHO (1997) reviewed several studies of pulmonary function in children exposed to NO_2 in indoor air. Ware et al (1984) found that gas cooking was associated with a 0.5% deficit in FEV_1 and FVC that was of doubtful significance. Neas et al (1991) found no association between children's lung function and NO_2. Dijkstra et al (1990) found a weak association between deficits in $FEF_{25-75\%}$ and NO_2 in children but not adolescents. FEV_1, PEF, $FEF_{25-75\%}$ in children were also associated with environmental tobacco smoke. Lebowitz et al (1985) found an association between gas cooking and decrements in PEF in both children and adults. Effects in adults were greatest for smokers. More recently, Ponsonby et al (2001) found no association between NO_2 exposure or gas appliance use and baseline lung function in Australian children. Personal NO_2 exposure was associated with a reduction in FEV_1/FVC after cold air challenge (-0.06% (96% CI -0.12% to –0.005%) per μgm^{-3} increase). Changes in this lung function measure were also associated with gas heater use. The results of a study of young British adults suggested an association between reduced FEV_1 but not FVC and gas cooking (Morgan et al, 1999).

The WHO (1997) also reviewed 3 studies of the effects of outdoor NO_2 concentrations on lung function. Dockery et al (1989b) found no association between lung function in children and NO_2, although an association was found between lung function and TSP. Schwartz (1989) found a significant association between lung function in adults and NO_2, but similar relationships were also found for TSP and ozone. In contrast Vedel et al (1987) found that NO_2 had no significant effects on lung function.

A number of more recent cross sectional studies of lung function in both children and adults have been performed (Table 7.3). Linn et al (1996) found no significant differences in the lung function of children in three communities with different levels of air pollution. Ackerman Liebrich et al (1997) reported an association between NO_2 and lung function in Swiss adults, but concentrations of NO_2 were well correlated with those of PM_{10}. Schindler et al (1998) found that the effects of variable NO_2 exposure on lung function in Swiss adults within a single community were smaller than those associated with intercommunity differences in NO_2 exposure. Decrements in lung function were significantly associated with personal exposure to NO_2 but not with outdoor concentrations. Particle concentrations were not investigated. Peters et al (1999) found significant associations between NO_2 and decrements in FVC and FEV_1 in Californian children and nonsignificant associations between NO_2 and decrements in PEFR and MMEF. Brunekreef et al (1996) and Hirsch et al (1999) found nonsignificant associations between NO_2 and lung function in Dutch and German children. Brunekreef et al (1996) found a stronger association between lung function and heavy traffic counts.

The results of the limited number of cohort studies of lung function in children have been generally similar to those of the cross sectional studies. Gauderman et al (2000, 2002) studied two groups of Californian school children. They found significant relationships between NO_2 and MMEF in both groups and also between NO_2 and FVC and FEV_1 in one of the groups. The apparent relationship between lung function and NO_2, however, disappeared in multipollutant models suggesting that NO_2 did not have an important independent effect. Avol et al (2001) found a nonsignificant association between lung function and NO_2 in a subset of children in the same Californian study that had changed place of residence. There was a closer association, however, between lung function and PM_{10}. Horak et al (2002) in a study of Austrian children found significant associations between wintertime NO_2 and decrements in lung function growth as assessed from FVC and FEV1 and nonsignificant associations between summertime NO_2 and decrements in FVC and FEV_1. The apparent effects of NO_2 were slightly enhanced in a two pollutant model with PM_{10}.

The factors governing lung function are complex and the effects of ambient air pollution may be small in comparison to those associated with personal exposure concentrations and other factors. Overall, the epidemiological evidence is suggestive of a weak association between NO_2 and long term changes in lung function. The effect is, however, extremely small. It is possible that the apparent effects of NO_2 on lung function are due to concurrent exposure to particles.

Table 7.3: Changes in lung function associated with long term exposure to NO_2

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
Switzerland Personal exposure to NO_2	FVC same community between communities	pers 27 ind 21 out 31				 -3.7 (-0.35- -7.05) -14.65 (-10.55 - -17.25)	na	Schindler et al (1998)
Swiss adults all never smoked	lung function FVC FEV1 FVC FEV1	35.6	21.2	11.7	43.1	 -1.19 -0.68 -1.22 -0.62	 -3.14 -1.03 -3.14 -1.06	Ackerman Liebrich et al (1997)
Southern California children (cross sectional study) 1994 air quality data	decrements in pulmonary function FVC FEV1 PEFR MMEF	41	34.9		64	 **9.7** (3.4) 4.7 (3.1) 6.2 (10.2) 6.9 (5.1)	 10.7 (6.9) 6.6 (5.5) 22.8 (16.1) 15.5 (8.1)	Peters et al (1999b)
Californian adolescents – cohort of individuals who had changed address	lung function FVC ml FEV1 ml MMEF ml/s PEFR ml/s	9-82	15-66		60-142	 -1.4 (-6.8-3.9) -4.3 (-9.4-0.7) -5.6 (-2.0-6.0)* -12.4 (-31.2-6.5)	 -1.8 (-9.1-5.5) -6.6 (-13.5-0.3) -16.6 (-32.1- -1.11) -34.9 (-59.8- -10.0)	Avol et al (2001)
Californian adolescents - cohort	% growth in lung function FVC FEV1 MMEF MMEF/FVC PEFR	9-82	15-66		60-142	 -0.04 (-0.12-0.05) -0.08 (-0.18-0.03) -0.18 (-0.32- -0.03) -0.14 (-0.27- -0.01) -0.03 (-0.19-0.13)	 -0.01 (-0.13-0.12) -0.04 (-0.20-0.12) -0.13 (-0.37-0.11) -0.12 (-0.32-0.07) -0.08 (-0.31-0.15)	Gauderman et al (2002)
Californian adolescents - cohort	% growth in lung function FVC FEV1 MMEF FEF75	9-82	15-66		60-142	 -0.08 (-0.14- -0.01) -0.11 (-0.20- -0.02) -0.15 (-0.30- -0.01) -0.20 (-0.39- -0.00)	 -0.11 (-0.22- -0.00) -0.17 (-0.31- -0.02) -0.36 (-0.47- -0.04) -0.32 (-0.61- -0.02)	Gauderman et al (2000)
Austrian schoolchildren – cohort	winter FVC mls-1day-1 FEV1 mlday-1	11.5ppb	21	16.8		 -0.000 -0.053	 0.01 -0.23	Horak et al (2002)

Location	*Population*	*Mean concentrations*				*% increase per increment (95% CI)*		*Study*
		NO_2	*PM_{10}*	*SO_2*	*O_3*	*NO_2 (10 μgm^{-3})*	*PM_{10} (10 μgm^{-3})*	
	MEF25-75 $mls^{-1}day^{-1}$ winter	6.7ppb	17.4	6.9		-0.215	-0.90	
	FVC					-0.156s	0.08	
	FEV1					-0.137s	0.01s	
	MEF25-75					-0.131	-0.08	

**appears to be an error in the original publication*

7.6 CANCER

There is very limited evidence to suggest that exposure to traffic pollution may be associated with some childhood cancers. Raaaschou Neilsen et al (2001) used NO_2 as a proxy for exposure to traffic pollution in a study of childhood cancer in Denmark. The risks of leukaemia, CNS tumours and "all cancers" were not related to concentrations of NO_2 or benzene. The risk of lymphomas, however, increased by 51% for a doubling of nitrogen dioxide concentrations during pregnancy. Effects were also seen for benzene. Feychting et al (1998) found a nonsignificant association between childhood cancer and exposure to motor exhaust as estimated from estimated NO_2 concentrations. A relative risk for all cancers of 2.7 (0.9-8.5) was estimated for children exposed to more than 50 μgm^{-3} NO_2 versus those exposed to less than 40 μgm^{-3}. For children exposed to more than 80 μgm^{-3}, the relative risk was 3.8 (1.2-12.1). Elevated risks were found for leukaemia and central nervous system cancers.

Several investigators have reported a possible association between exposure to airborne particles and increased lung cancer risks. There is much less evidence to link exposure to NO_2 with lung cancer. Diet may have an important confounding effect on lung cancer risk (Koo and Ho, 1996). A Swedish study (Nyberg et al, 2000) found an association between lung cancer risk and average traffic related NO_2 (as a marker of traffic pollution) over 30 years. NO_2 exposures were estimated using source estimates and dispersion modelling. The relative risk for the 10% of the study population with the greatest estimated NO_2 exposure twenty years earlier was 1.4 (1.0-2.0). A Japanese study (Choi et al, 1997) found that regional differences in age-adjusted lung cancer death rates were associated with NO_2 and temperature (other variables examined were SO_2, motor vehicle density, tobacco expenditure). Temperature increased the effects of NO_2 in combined models. Given that particles were not considered, it is not possible to link effects specifically with NO_2. Beeson et al (1998) found that there was a nonsignificant association between NO_2 and the incidence of lung cancer in males in the Californian 7th Day Adventist Cohort whereas Abbey et al (1999) found a significant association between NO_2 and lung cancer mortality in females (Tables 7.1, 7.4). Concentrations of NO_2 were moderately correlated with those of PM_{10} (r = 0.57). The results of both studies suggest a large apparent effect of NO_2 on lung cancer risk, but the confidence intervals were extremely wide. The results of the two studies are also inconsistent with respect to the relative risks of lung cancer incidence and mortality for males and females although this could reflect differences in survival following diagnosis.

Table 7.4: Other health endpoints

Location	***Health endpoint***	***% increase per increment (95% CI)***		***Study***
		NO_2 (10 μgm^{-3})	***PM_{10} (10 μgm^{-3})***	
USA	lung cancer (incidence)	119 (-9-567)	175 (39-541)	Beeson et al (1998)
Czech Republic	low birth weight stillbirth	1.4 (-0.4-3.2) NO_x none	**0.8** (0.4-3.4) TSP none	Bobak and Leon (1999)

Overall, the evidence linking NO_2 to various cancers is relatively weak. There is very limited evidence linking traffic pollution to some childhood cancers, but given that traffic fumes include a range of proven carcinogens such as benzene and PAHs, NO_2 is unlikely to be the causal agent. The results of studies of lung cancers in adults are inconsistent.

7.7 OTHER EFFECTS

7.7.1 Effects on the unborn child

There have been a few studies of the possible effects of air pollution on the unborn child. These studies face a general difficulty in distinguishing the effects of air pollution from other environmental pollutants and the effects of socioeconomic status. Ha et al (2001) in a study of mothers in Seoul, South Korea found that the risk of low birth weight was associated with exposure to air pollution during the first trimester of pregnancy. Significant relative risks were associated with interquartile increases in carbon monoxide, nitrogen dioxide, sulphur dioxide and TSP. Bobak and Leon (1999) also found an association between low birth weight and air pollution, but effects were not specific to NO_2. In a multi-pollutant model, only SO_2 remained significantly associated with birth weight. The results of this study are difficult to interpret because of the severe confounding effects of socioeconomic status. Ritz et al (2000) reported that exposure to NO_2 not associated with pre-term birth in Southern California.

Overall there is no clear evidence that exposure to nitrogen dioxide has an adverse effect on pregnancy outcome.

7.7.2 Effects on antioxidant status

A Mexican study found that serum superoxide dismutase activity and thiobarbituric acid-reactive materials were higher in adults who and recently moved to Mexico City than in those that had never lived there or those who had lived there throughout their lives (Hicks et al, 1996). This is consistent with adaptation on long term exposure to NO_2.

7.8 DISCUSSION

7.8.1 Exposure assessment

The effects of long term exposure to air pollution are difficult to investigate because of the difficulty in adequately characterising exposure. Most available studies are cross sectional in design rather than longitudinal and therefore do not allow for the movement of individuals between areas with differing levels of pollution in earlier years nor for the change in pollution mix over recent years.

Exposure assessment is particularly difficult in investigations of the effects of NO_2 because of the importance of both indoor and outdoor sources in determining personal exposure concentrations. These problems are compounded when smokers are considered, as their exposure is dominated by the effects of inhaling tobacco smoke which contains substantial quantities of NO_x. In short term investigations, it may be possible to investigate personal exposures to NO_2, but it is much more difficult to establish long term personal exposure concentrations. In one study where some estimation of personal exposure concentrations was made, a much stronger association was found between personal exposure to NO_2 and lung function than between outdoor concentrations of NO_2 and lung function (Schindler et al, 1998). Smoking is likely to have a substantial impact on personal exposure to NO_2 in the populations that have been the subject of longitudinal or cross sectional epidemiological studies. For smokers, the effect of changes in ambient NO_2 concentrations on personal exposure would be negligible in comparison with that for nonsmokers. Given that about half of the general population are active smokers, this means that about half of a typical study population would be unlikely to be affected by small changes in ambient NO_2 (section 3.8.1). This will have substantially weakened the power of epidemiological studies to detect the effects of changes in ambient NO_2. It is probable that most of any effects of NO_2 would be

concentrated in nonsmokers. The size of any effect in nonsmokers would be greatly reduced when averaged across the whole population.

Many studies of the relationship between NO_2 and respiratory symptoms have focussed on indoor air quality. These studies are of limited value in assessing the value of policies designed to control outdoor concentrations of NO_2. As with studies of ambient NO_2 concentrations, it is difficult to know whether observed effects are specifically with NO_2 or whether NO_2 is acting as proxy for other indoor pollutants. The studies that have used gas cooking as a proxy for NO_2 exposure are of limited value in determining whether NO_2 is specifically associated with adverse effects on health. It is plausible that indoor concentrations of NO_2 are strongly correlated with those of ultrafine particles given that gas cooking, tobacco smoke and outdoor air are all important sources of indoor ultrafine particles and influences on NO_2 concentrations (sections 3.4, 3.7). It seems likely, however, that the ratio of concentrations of NO_2 to those of ultrafine in outdoor air, fumes from cooking and tobacco smoke would be variable. The overall ratio of concentrations of NO_2 to those of ultrafine particles indoor air would differ from those of outdoor air and would also differ between different indoor environments.

In conclusion, poor exposure characterisation in epidemiological studies of the long term effects of NO_2 is likely to have reduced the power of these studies to find effects and may have given rise to underestimation of the size of any effects. In the future, the use of modelling to improve individual exposure estimates for NO_2 and ultrafine particles, may greatly increase the power of these studies to detect effects.

7.8.2 Attribution of effects

Ambient concentrations of NO_2 are generally strongly correlated with particles so that there is difficulty in the attribution of effects specifically to NO_2 or particles, as previously discussed for short term effects. The problem may be compounded in studies of long term effects because the exposure variable is place rather than time giving rise to a fewer number of data points. Events leading to short term independent variability in the concentrations of either particles or NO_2 that might arise in time series studies would be lost in the determination of long term mean exposure concentrations. Even where NO_2 does not appear to be strongly correlated with PM_{10}, it is difficult to be certain that effects attributed to NO_2 are not due to confounding by some unmeasured co-pollutant. The main sources of ambient NO_2 are high temperature combustion processes that also generate substantial quantities of ultrafine particles. These ultrafine particles only form a tiny component of total particle mass and therefore may not be strongly correlated with PM_{10}, the normal metric of fine particle concentrations. Even in the ACS study, where $PM_{2.5}$ rather than PM_{10} was the metric of particle concentrations, it is difficult to know what proportion of $PM_{2.5}$ was composed of ultrafine primary particles generated by combustion, as opposed to secondary sulphate.

NO_2 concentrations are heavily influenced by photochemical reactions in the atmosphere. The failure of the ACS study to find a relationship between mortality and NO_2 strongly suggests that the influence of long term exposure to NO_2 on life expectancy is very small. It does not necessarily imply that the observed effects with $PM_{2.5}$ were not largely caused by ultrafine. Concentrations of NO_2 and ultrafine particles are unlikely to be well correlated in North America, where extensive photochemical activity would be expected to occur during the summer months.

There are relatively few studies of the effects of long term exposure to NO_2. There is therefore insufficient information to determine whether the apparent effects of NO_2 show a consistent variation in different pollutant mixes that might reflect the role of NO_2 as a proxy for some other pollutant that actually caused the observed effects.

Much of the information linking NO_2 and respiratory symptoms has been derived in studies of indoor air quality and it is difficult to know whether associations with NO_2 reflect a genuine influence of NO_2 on respiratory health, or the effects of co-pollutants including nitrous acid. Nitrous acid forms readily as a product of NO_2 emissions within indoor environments and not all measurement techniques are able to distinguish NO_2 from nitrous acid (section 3.2). Gas cooking is also a substantial source of ultrafine particles (Denekamp et al, 2001). Toxicological experiments have demonstrated that ultrafine particles could have a substantial effect on the respiratory system at relatively low levels of exposure (EPAQS, 2001), whereas toxicological investigations of NO_2 have only found adverse effects at relatively high levels of exposure (Ch 4). The few studies that have examined both gas cooking and nitrogen dioxide exposure as independent variables affecting respiratory health have not shown consistent effects. The Singapore study that showed an association between respiratory symptoms and cooking fume, may however, be indicative that the apparent effects of gas cooking on respiratory health are largely due to fine particles.

Overall, the results of epidemiological studies suggest an association between traffic emissions and adverse effects on respiratory health that may be due to NO_2. There is also some evidence of a link between indoor air quality and respiratory health that may be due to NO_2, but might be related to some other component of emissions from gas cooking.

7.8.3 Relevant health endpoints and public health importance

The results of epidemiological studies have suggested associations between long term exposure to NO_2 and a range of health endpoints, but the results of individual studies are inconsistent. The health endpoints for which the evidence of an association with NO_2 is most consistent are respiratory symptoms, including bronchitis, and lung function. It is possible that NO_2 may contribute to a small loss of life expectancy associated with long term exposure to ambient air pollution. Although the results of a number of studies have suggested a link between NO_2 and respiratory symptoms in children, the evidence is inconsistent and relies heavily on studies of gas cooking suggesting that observed effects could be due to exposure to some other product of gas combustion. It is not possible, however, to eliminate the possibility that NO_2 is associated with respiratory symptoms in children. Overall, the influence of ambient NO_2 on health appears to be much smaller than that of ambient particles

7.9 CONCLUSIONS

The difficulty in determining personal exposures to NO_2 over prolonged timescales has made the determination of the effects of long term exposure to NO_2 in epidemiological studies relatively difficult. There are many fewer studies of the long term effects of NO_2 than of the effects of day to day fluctuations of ambient concentrations.

The results of the limited number of studies available suggests that long term exposure to NO_2 may lead to slightly increased risks of respiratory symptoms, including bronchitis and a small reduction in lung function growth in children and lung function in adults. Long term exposure to NO_2 may also lead to a small loss of life expectancy, but the evidence for this is weak. It is difficult to be certain to what extent apparent effects are due to NO_2 and not concurrent exposure to particles. It is also possible that NO_2 is a proxy for some other causal agent such as ultrafine particles.

8. QUANTIFICATION OF HEALTH EFFECTS ASSOCIATED WITH AMBIENT NO_2 IN THE UK

8.1 INTRODUCTION

This chapter describes the potential burden of ill-health in the UK that might be attributed to exposure to ambient NO_2. This includes the effects of the potential modification of the relationship between PM_{10} and daily mortality by NO_2. A brief review is also made of the potential impacts of other pollutants formed as a result of secondary reactions of NO_x in the atmosphere. The initial part of the chapter describes the concentration-response functions selected for quantification and background levels of the health points of interest in the UK population. The remainder of the chapter describes the potential scale of effects. Given the uncertainties in the concentration-response functions, a range of estimated impacts is given for each health endpoint. A key problem with the quantification reported here is uncertainty as to whether the estimated effects are truly due to NO_2 rather than a reflection of the impacts of traffic pollution more generally (see section 6.12, 7.8).

A spreadsheet was used to link population data, pollution data, concentration-response functions and background levels to calculate the total impact for each health endpoint. Although there are uncertainties with respect to the linkage of these concentrations to the census population data, these were considered to be small in comparison to those associated with the selection of concentration-response functions.

Effects have been estimated relative to natural background concentrations as found in remote rural areas (5 μgm^{-3}). There has been a substantial fall in NO_2 concentrations since 1990 and a further fall in NO_x emissions in traffic will lead to a more modest reduction in NO_2 concentrations by 2010. Emissions from other combustion sources may increase slightly during the next few years. Further substantial cuts in NO_2 concentrations are unlikely with existing technologies.

8.2 ESTIMATED LEVELS OF EXPOSURE

The quantification was based on 2001 census data. An estimate of current annual mean concentrations of NO_2 in each local authority area was made using the maps published on the www.airquality.co.uk website and measured annual mean concentrations in 1998 at various monitoring sites as listed by DETR et al (2000). Similar estimates were made for PM_{10} but using monitoring data for 2000 reported by DEFRA et al (2001). At the time the quantification was undertaken (January 2003), these sources provided the most up to date summary of annual mean concentrations that was readily available in the public domain. More information is now available at www.airquality.co.uk, but it is still difficult to access this information in an efficient manner to undertake a UK-wide quantification. A population weighted annual mean concentration was used to estimate the impacts of short term variations in NO_2 for a 12 month period (following COMEAP, 1998). This may not completely capture the impacts of peak pollution events as there is only a moderate correlation between annual mean concentrations of NO_2 and the frequency and intensity of high pollution events (see section 3.3.2). The population mean exposure for NO_2 in 1998 was estimated as 25.6 μgm^{-3}. The estimated population mean exposure was greatest in the Greater London area, 41.0 μgm^{-3}, and lowest in the Scottish Highlands, 5 μgm^{-3}.

8.3 SELECTION OF CONCENTRATION-RESPONSE FUNCTIONS

Table 8.1 shows the concentration response functions used in the quantification. These were derived from the literature review. The application of these concentration-response functions assumed that there is no threshold for effects and that the variability of NO_2 concentrations is of more importance than the intensity and frequency of high pollution events (although these should be correlated). We identified four levels of certainty:

1. Highly certain - effects for which there is reliable concentration-response information and good information about background rates.

2. Fairly certain – effects for which the concentration-response information seems plausible in the light of other information and there is reasonable information about background rates.

3. Moderately uncertain – effects for which we are unsure about whether effects are correctly attributed and/or where the source concentration-response information is from small studies that may not be directly applicable to the Scottish population. The combination of effects with uncertainties 1, 2 and 3 may give a slightly high estimate of total effects.

4. Very uncertain – effects for which the concentration-response information is very uncertain. The combination of effects of uncertainties 1, 2, 3 and 4 is likely to overestimate effects.

None of the concentration-response information used in the quantification could be said to be highly certain. One of the main causes of uncertainty is that NO_2 is a good indicator of traffic pollution and effects attributed to NO_2 in epidemiological studies may be due to some other component of traffic pollution.

Table 8.1: Concentration-response functions used in quantification

Health endpoint	***Concentration-response function %change/µgm^{-3}***	***Certainty***	***Comments***
acute mortality	0.05	2	many studies, but findings variable
hospital admission – respiratory	0.07	2	many studies, but findings variable
hospital admission – cardiac	0.07	2	many studies, but findings variable
GP consultations for respiratory illness	0.23	3	few studies relevant to UK
symptom days per person – respiratory symptoms	0.5	4	many studies, findings very variable, uncertainty in baseline information
days of acute respiratory illness per person	0.5	4	single study, association lacked statistical significance, uncertainty in baseline information

8.4 BACKGROUND INCIDENCE/PREVALENCE OF HEALTH ENDPOINTS OF INTEREST

8.4.1 Mortality

The "all cause" death rate for England and Wales 1998 was 1025.7/100 000 population (IGCB). The corresponding death rate for Scotland in 1999 was 1180/ 100 0000 (ISD website). In the UK as a whole, 24% of deaths were due to respiratory illness, 21% due to coronary heart disease, 10% due to stroke and 8% due to other cardiovascular disease (British Thoracic Society 2001). Lung cancer accounted for just over 22% of deaths from respiratory causes in 1999. The lung cancer death rate in 2000 was 68.2 per 100 000 (DoH website).

8.4.2 Hospital admission

In England and Wales (1999-2000), the rates of emergency admission to hospital for respiratory and cardiovascular illnesses were 942/100 000 and 733.7/100 000 respectively (IGCB).

8.4.3 GP consultation

In England and Wales (1999-2000), the rates of GP consultations for respiratory illness (including multiple consultations by individual patients) were 104.82/ 100 population for children under 16 years in age, 48.5/100 for adults aged 16-64 years, 68.79/100 for adults aged 65 to 74 and 71.09/100 for adults over 74 (British Thoracic Society, 2001). This gives an average of about 64/100. Other estimates of rates of GP consultation are somewhat lower. The National Asthma Campaign (www.sghms.ac.uk/phs/laia/laia.htm) estimate that for every 1000 children, there are 140 GP consultations for asthma and 50 consultations for bronchitis each year. A London study found that the average number of GP consultations for lower respiratory symptoms was 4.599/100 population for asthma and 10.185/100 population for lower respiratory symptoms (Hajat et al, 1997).

8.4.4 Respiratory symptoms and acute respiratory illness

It is extremely difficult to estimate the incidence of respiratory symptoms in the general population or among asthmatics. The panel studies that have investigated the effects of air pollution on respiratory health have been small and may not be representative of children or asthmatics more generally. There is a paucity of information about symptoms in nonasthmatic adults. There is a small amount of further information available from the British Thoracic Society, the National Asthma Campaign and the Department of Health, but none of these sources provide clear information about the prevalence of acute respiratory symptoms within the general population or asthmatics.

The incidence of respiratory symptoms in different panels is highly variable (Table 8.2). On the whole, the average number of symptom days for cough in adult asthmatics who have taken part in panel studies is about 60 days/year and for wheeze only about 30 days/year. The average number of days on which bronchodilators are used is about 150/adult asthmatic/year. It is not clear how representative this would be of asthmatic adults generally. For children, the average number of symptom days for upper respiratory symptoms varies from about 15 to 131 for asthmatic children. On the whole, the results of the various panel studies suggest that 70 symptom days/asthmatic child/year is a reasonable estimate of background prevalence.

Table 8.2: Incidence of respiratory symptoms in panel studies

Health endpoint	*Incidence/person/year*	*Study*
symptom days – asthmatic adult		Dusseldorp et al (1995)
cough	67.5	
runny nose	25.2	
wheezing	29.6	
bronchodilator use	159.9	
symptom days – asthmatic child	63.9*	Pope and Dockery (1992)
symptom days – asthmatic child		Linaker et al (2000)
upper respiratory symptoms	34.0	
symptom days – asthmatic adult		Neukeirch et al (1998)
asthma attack	33.6	
wheeze	55.1	
shortness of breath	166.8	
symptom days-children		van der Zee et al (1999)
those with symptoms		
lower respiratory symptoms	32.2	
upper respiratory symptoms	130.8	
cough	127.8	
phlegm	63.3	
bronchodilator use	79.4	
those without symptoms		
lower respiratory symptoms	3.5	
upper respiratory symptoms	80.8	
cough	62.5	
phlegm	24.7	
Adult asthmatics		Penttinen et al (2001)
cough	107.3	
symptoms	116.4	
bronchodilator **doses**	1679	
Adult asthmatics		Hiltermann et al (1998)
shortness of breath	158.4	
cough and/or phlegm	125.9	
nasal symptoms	198.2	
bronchodilator use	117.2	
symptom days – children		Timonen and Pekkanen 1997 Finland
those with asthma	14.7	
those with cough not asthma	12.4	
bronchodilator use in asthmatic children	21.1	

**ExternE assumed that the background prevalence of respiratory symptoms in European children was half that cited by this study for US children*

The National Asthma Campaign estimate that for every 1000 children, 22 have more than 12 asthma attacks each year, 43 are woken at least once each week by wheeze and 150 will have experienced wheeze within the last year. Averaged across all children, this gives a minimum of 2.343 symptom days/ child/year (assuming that the 2.2% that have more than 12 attacks each year are also woken at least each week). Most asthmatic attacks last several days. For example Linaker et al (2000) found that the average length of attack in 114 asthmatic children was 9.2 days and the median length about 5 days. It seems likely therefore that a child experiencing 12 attacks in a year would experience at least 60 symptom days a year and probably more than 100 symptom days a year. Children experiencing an episode of wheeze are likely to have at least 5 symptom days per year. This would suggest that the average number of symptom days per asthmatic child per year is likely to be more than 20 and

probably more than 27. This is at the low end of the incidence rates found in panel studies. Averaged across all children, it implies an average number of 3 symptom days/child/year.

The British Thoracic Society's report implies that the prevalence of acute bronchitis was 0.676 for men and 0.834 for women per 100 population in 1991/92. This gives an average number of symptom days/adult/year of 2.5 for men and 3.0 for women.

The DoH's survey of the nations health (Indicators of the Nations Health, www.doh.gov.uk/HPSSS/TBL_A5.HTM) found that 15% of men and 19% of women had experienced an acute sickness (of any type) in the two weeks preceding the interview. This gives an annual incidence of acute sicknesses (of any type) of at least 468/100 adults. If GP consultations are used as a guide to the likely proportion of these sicknesses were of respiratory system, then the inferred number of episodes of acute respiratory illness in adults would be 75/100 adults. If it is assumed that each illness lasts 3 days – a typical cold – then this implies 2.25 days of acute respiratory illness/adult/ year. This excludes the effects of long term illness. In the absence of better information a background rate of 2.25 restricted activity days/person/year arising from acute respiratory illness was assumed for the purposes of quantification. This is similar to the British Thoracic Society's average number of symptom days per adult for acute bronchitis alone, suggesting that it is an underestimate of the true levels of restricted activity arising from respiratory illness.

8.4.5 Use of medication

Although there is insufficient concentration-response information available to allow estimation of the effects of NO_2 on the use of medication for respiratory illness, the background rates of medication use were reviewed in order to inform estimation of background rates of other health endpoints. The prescription rate for medicines to prevent and treat respiratory disease was 90/ 100 population for men and 92.9/ 100 population for women (British Thoracic Society, 2001). Bronchodilators represented almost 50% of all prescriptions (49.8%) and inhaled corticosteroids represented 24.4% of all prescriptions. The number of doses per prescription is variable (British Thoracic Society, 2001). Bronchodilators vary from 60 –200 doses, although many brands have about 100 doses. The British Thoracic Society estimate that 12% of adults are treated for asthma, giving an implied prescription rate of about 3.75 bronchodilators/asthmatic per year or about 1 dose/asthmatic/day.

8.4.6 Long term respiratory illness

Different reports give very different impressions of the prevalence of chronic respiratory conditions (Tables 8.3, 8.4). This may be partly because many asthmatics have relatively mild symptoms and may only rarely visit their GP for advice and new medication. We have previously estimated that 5% of adults are asthmatic and 10% of children (Scottish Executive study). The British Thoracic Society suggest that the prevalence of asthmatic symptoms may be closer to 20% in both adults and children. More than 10% of adults and 20% of children are reported to receive treatment for symptoms of asthma. About a third of the population may show asthmatic symptoms at some stage in their lives. For the purposes of this study, 10% of both adults and children were assumed to be asthmatic. This may give a slight underestimation of effects, particularly with respect for children. Most UK estimates of the prevalence of chronic bronchitis are low (less than 2%) compared with US estimates (5-8%). One UK source, however, suggests that about 7% of adults under 65 and 12% of those older than 65 have symptoms of chronic bronchitis. This seems a more realistic estimate of prevalence, given the importance of respiratory illness as a cause of hospital admission and death. One US panel study found that the prevalence of chronic cough in children was 5.8% and that of bronchitis was 6.5% (Schwartz, 1993).

Table 8.3: Prevalence of long term respiratory illness (as a percentage of all men, women, children) – national data sources

Condition	*UK - BTS (2001)*	*US - 1996*
Respiratory illness (all)		
men	7.2	
women	7.6	
Asthma		
men – treated 1991-92	4.2	
women – treated 1991-92	5.6	
men 1995/1996	11	3.75
women 1995/1996	12	5.13
all adults 1995/1996	12	
boys	23	
girls	18	
all children	21	
children	13*	
children on bronchodilators	13.3*	
children on inhaled steroids or comoglycate	4.7*	
Ever wheezed		
men 1995/1996	35	
women 1995/1996	31	
all adults 1995/1996	33	
boys	31	
girls	26	
all children	28	
Wheezed in last 12 months		
men 1995/1996	21	
women 1995/1996	20	
all adults 1995/1996	21	
boys	20	
girls	17	
all children	18	
Bronchitis and emphysema		
men	1.3	8.2
women	0.7	10.6
Chronic bronchitis		
men		4.88
women		7.41
adults 15-64	7	
adults 65+	12	
Hay fever		
men	0.6	
women	0.5	
Other respiratory		
men	1.1	3.75
women	0.8	5.31
Self reported long term respiratory illness		
men	9.2	
women	9.5	
boys	14.1	
girls	10.0	
GP treated respiratory disease		
all	3.07	
asthma		
men	0.429	
women	0.422	
acute bronchitis		
men	0.676	
women	0.834	
chronic bronchitis		
men	0.054	
women	0.037	

**National Asthma Campaign*

Table 8.4: Prevalence (percentage) of long term respiratory illness – panel studies

Health endpoint	*Prevalence*	*Study*
Schoolchildren (842)		Shima and Adachi (2000)
Bronchial asthma	5.8	
History of allergic disease	50.4	
Respiratory disease under 2 years of age	9.0	
Dutch children: polluted area		de Kok et al (1996)
ever cough	37.5	
current cough	16.5	
ever shortness of breath	17.5	
current shortness of breath	15	
ever wheeze	31	
current wheeze	16	
ever asthma	6.5	
ever bronchitis	34.5	
current asthma medication	3.5	
Dutch children: less polluted area		
ever cough		
current cough	25	
ever shortness of breath	4.5	
current shortness of breath	11	
ever wheeze	7.5	
current wheeze	25	
ever asthma	13	
ever bronchitis	6	
current asthma medication	28	
	3.5	
Australian schoolchildren (344)		Ponsonby et al (2001)
History of asthma	39	
Wheeze in last 12 months	28	

8.4.7 Summary of background rates used in quantification

Table 8.5 summaries the background rates for the health endpoints considered in the quantification.

Table 8.5: Background rates for the health endpoints considered in the quantification.

Health endpoint	*Number of cases/ 100 population/ year*	*UK baseline – annual rates*
acute mortality	1.0257	603 000
hospital admission – respiratory	0.942	553 800
hospital admission – cardiac	0.7337	481300
GP consultations for respiratory illness	64.13	3 770 000 000
symptom days in asthmatics respiratory symptoms*	600	705 500 000
restricted activity days due to acute respiratory illness per person (all)	225**	132 300 000

**assumes 10% of population has asthma*
*** probable underestimate*

8.5 DIRECT EFFECTS OF NO_2

8.5.1 Short term effects

The estimated short term effects of NO_2 on a range of health endpoints is shown in Table 8.6. Two estimates are shown for each endpoint. The estimate based on the best concentration response relationship from single pollutant models is likely to be an upper bound estimate of potential effects. The actual contribution of NO_2 to effects is likely to be smaller. In many studies, the apparent effects of NO_2 disappear in multipollutant models. It seems highly unlikely that NO_2 has no impact at all on health and the lower bound estimate of potential effects has been arbitrarily calculated as 10% of the upper bound effect. It is probable that actual impacts are closer to the lower bound than the upper bound estimate.

Table 8.6: Estimated impact of anthroprogenic NO_2 on health within the UK (includes sources both within and external to the UK)

Health endpoint	***UK baseline – annual rates***	***lower bound estimate of impacts that may be attributable to NO_2***	***maximum increment that may be attributable to NO_2***
acute mortality	603 000	620	6 200
hospital admission – respiratory	553 800	800	8 000
hospital admission – cardiac	481300	620	6 200
GP consultations for respiratory illness	3 770 000 000	203 600	2 036 000
symptom days – asthmatics	705 500 000*	6 640 000*	36 400 000*
restricted activity days due to acute respiratory illness	132 300 000	1 370 000	13 700 000

**assumes 10% of the population has asthma*

The results of the quantification suggest that NO_2 has a small effect on daily mortality. These extra deaths are thought to represent deaths brought forward by a few weeks rather than years. The effect on hospital admissions is also small. More substantial impacts are seen for GP consultations and on the numbers of days individuals experience respiratory symptoms. The maximum estimate of the number of extra days of respiratory symptoms experienced by individual asthmatics is 7 days/person/year or 0.7 days/person/year if effects are averaged across the whole population. The maximum estimate of the number of extra days of acute respiratory symptoms is equivalent to 0.2 days/person/year. The effects on asthmatic symptoms may be underestimated as baseline prevalence of asthma may be greater than 10%.

The estimated short term impacts of NO_2 are likely to be unevenly distributed in time and space (see Chapter 3). Impacts are likely to be slightly greater during the winter than during the summer as a result of higher mean exposures to NO_2. They are also likely to be greater in the highly populated Greater London area than elsewhere in the country and least in sparsely populated remote rural areas where concentrations of NO_2 are low (Chapter 3).

8.5.2 Long term effects of NO_2

There is considerable uncertainty about the long term effects of exposure to NO_2. There is no reliable concentration-response information for mortality and it is apparent that the effects of NO_2 on life expectancy are small in comparison to those of particles.

There is also no reliable concentration-response information linking NO_2 to chronic respiratory illness. The information that is available suggests that an increase in NO_2 concentrations of 10 μgm^{-3} is associated with an increase of about 10% in the prevalence of chronic respiratory illness. Given a baseline prevalence of about 7% for respiratory illness in the general population, this implies that about 850000 individuals or 1.4% of the population have long term respiratory illnesses that may be attributable to NO_2. There is a very high level of uncertainty associated with this estimate.

8.6 INDIRECT EFFECTS OF NO_2

8.6.1 Ozone

UK emissions of NO_x contribute relatively little to UK concentrations of ozone, although they are likely to have a substantial impact on Mainland Europe. It seems likely that the impact of UK emissions of NO_x on the total burden of ill health in the UK due to ozone is small, although the impacts in mainland Europe may be more significant.

The calculation of the health impacts of ozone is uncertain because some authors have suggested that effects are only found above a threshold level of exposure. In 1998, COMEAP estimated that during the summer of 1995, exposure to ozone may have contributed to 700 deaths brought forward and 500 hospital admissions, if a 100 μgm^{-3} threshold for effects was assumed. If no threshold was assumed, then ozone may have contributed to 12 500 deaths brought forward and 9 900 hospital admissions. During recent years, average concentrations of ozone have increased but the number of peak exposures has decreased. The impacts on health are unclear.

8.6.2 Acidity

UK emissions of NO_x contribute to aerosol acidity but the importance of aerosol acidity in the relationship between PM_{10} and health effects is uncertain. Most reviewers have concluded that acidity does contribute to the observed effects of PM_{10}, but adverse effects have been associated with PM_{10}, even in the absence of aerosol acidity. A few studies have suggested a possible link between concentrations of nitrous or nitric acid vapour and respiratory health in children. There is too little information to reliably quantify the impacts of nitrous and nitric acid vapour in UK air.

8.6.3 Nitrate

Secondary nitrate accounts for about 10% of the mass concentration of PM_{10}, but is unlikely to account for 10% of the potential health impact of PM_{10}. There is no epidemiological evidence that concentrations of nitrate particles have an important influence on health. Toxicological investigations involving animal and human exposures to nitrate particles have failed to find effects at concentrations that are hundreds of times greater than those in ambient air. Nitrate particles deposited on the surfaces of the airways or lung would rapidly dissolve and the component ions would become indistinguishable from those already present in tissue and body fluids. The health impact, if any, associated with ambient nitrate particles is likely to be associated with any non-nitrate component of the particles. Some nitrate particles, for example, may nucleate on ultrafine particles from vehicle exhaust and other combustion processes and will therefore contain species such as polyaromatic hydrocarbons. Given that nitrate particles are generally well within the respirable size range, they might have importance in transporting absorbed species to the alveolar region of the lung. There is little information about the nature and toxicity of secondary nitrate particles. It is difficult therefore to determine how much, if any, of the impacts of PM_{10} can be attributed to nitrate, but it might be reasonable to assume that for nitrate the increase in effects per μgm^{-3} would be less than

half that estimated for total PM_{10}. Given that nitrate comprises about 10% of the mass of PM_{10}, its impact is possibly (at most) about 5% of that of PM_{10} as a whole and possibly of similar importance to the direct impact of gaseous NO_2. Only some of this impact will be due to NO_x emitted within the UK and improved control of NO_x emissions in the UK will have little effect on the impacts of secondary nitrate particles in the UK, although there would be benefits for mainland Europe.

8.6.4 PAN and other organo-nitrate compounds

The UK concentrations of secondary organic species formed as a result of NO_x emissions are well below the levels at which any health effects would be likely, even during periods of peak photochemical activity.

8.6.5 Effects of NO_2 on particle impacts

The results of the second phase of the APHEA study (Katsouyanni et al 2001) suggest that NO_2 has an important modifying effect on the relationship between particles and daily mortality, with particle impacts being increased at high concentrations of NO_2. This finding has not been borne out by the results of other studies and there have been no comparable findings in studies of other health endpoints. There is therefore extreme uncertainty about the potential for NO_2 to modify particle effects. If, however, the APHEA results are used to estimate the potential impact of NO_2 on particle-related daily mortality, the implied indirect impact of NO_2 on particle-related mortality leads to a doubling of estimated number of deaths brought forward as a result of PM_{10}. This implied indirect effect of NO_2 is five times greater than the direct impact of NO_2 on mortality.

Endpoint	Number of deaths brought forward per annum
Particle-related daily mortality, excluding any effects of NO_2	32 938
Particle-related mortality adjusted for effects of NO_2	70 196

8.7 SOURCES OF UNCERTAINTY IN ESTIMATION OF IMPACTS

There is considerable uncertainty in the estimation of the direct impacts of exposure to ambient NO_2 in the UK. Sources of uncertainty include:

1. reliability of exposure estimates and the relationship of personal exposure to ambient NO_2 to estimated population mean concentrations;
2. importance of ambient NO_2 in governing personal exposure to NO_2;
3. the extent to which high pollution events are important in determining actual effects and whether the use of annual mean concentrations to estimate effects adequately captures the influence of high pollution events;
4. uncertainties in the concentration-response functions available, particularly as to whether effects attributed to NO_2 are actually due to gaseous NO_2 as opposed to being caused by some other component of the pollution mix that is strongly correlated with NO_2;
5. Uncertainties in the baseline prevalence or incidence of the health endpoints of interest.

The issues with respect to exposure estimation were discussed in full in Chapter 3. These uncertainties relate not only to the estimation of the impacts of NO_2 within the UK, but also impinge on the reliability of exposure estimates used in the epidemiological studies from which concentration-response functions have been derived. The results of the animal and

human toxicological experiments described in Chapters 4 and 5 underline the potential importance of short term (1 hour) peaks in exposure. These peaks of exposure may not be adequately captured by the use of annual mean concentrations to estimate effects, although there is a moderate correlation between annual mean and peak concentrations (Chapter 3). The results of toxicological and human volunteer studies suggest that the frequency and intensity of high pollution events may be more important than the simple variability of NO_2 concentrations through time.

There is considerable uncertainty as to whether NO_2 is the causal agent of effects described in epidemiological studies. The results of the animal and human experiments described in Chapters 4 and 5 strongly suggest that the adverse effects of NO_2 on respiratory health, only arise above a threshold level of exposure. This suggests that the effects attributed to much lower concentrations of NO_2 in epidemiological studies could have been caused by another pollutant, most probably another component of traffic emissions. The upper bound estimates of the effects of NO_2 presented in this chapter may be better described as estimates of the effects of traffic pollution that would include not only NO_2 but other pollutants such as ultrafine particles. Given the oxidative properties of NO_2, however, and the potential importance of reactive oxygen species in giving rise to the adverse respiratory effects associated with air pollution, it seems likely that at least some of the effects of traffic pollution are attributable to NO_2 and therefore the lower bound estimates have been estimated as 10% of the upper bound estimates of effects rather than as zero. Effects may have been considerably over-estimated if there is a threshold concentration below which NO_2 has no influence on respiratory health.

The main uncertainty in the estimation of baseline rates for use in quantification was in the identification of appropriate baseline rates of respiratory symptoms and long term respiratory illness in the UK population.

There estimation of the indirect impacts of NO_2 on health in the UK is even more uncertain than the direct effects. The uncertainties associated with the estimated impacts of nitrate, ozone and the interaction of NO_2 and particles are discussed separately below.

There are uncertainties in the exposure estimates for nitrate. It is not clear how great the impact of UK emissions of NO_2 is on total population exposure to particulate nitrate/PM_{10} in Western Europe. Although there is limited information that allows estimation of mean population exposure to nitrate in the UK (section 3.4), there is very little toxicological or epidemiological information about the potency of nitrate relative to other components of PM_{10}. The highly soluble nature of nitrate particles and their small contribution to biological levels of ammonium, nitrate and other ions suggests that they are likely to be much less toxic than other components of PM_{10}. There is no quantitative information specific to nitrate from which a concentration-response function could be derived and therefore there is huge uncertainty in the assumed potency of nitrate versus that of total PM_{10}.

Many of the sources of uncertainty associated with the estimation of population exposures to nitrate in the UK also apply to ozone. There is uncertainty in attributing ozone formation in the UK and elsewhere in Europe to UK emissions of NO_2. There is also uncertainty in the application of concentration-response information for ozone and whether a threshold level of exposure should be assumed.

The major source of uncertainty with respect to estimating the extent to which NO_2 may modify particle impacts is that the concentration-response information comes from a single epidemiological study (Chapter 6).

Overall, the main source of uncertainties associated with the quantification of the direct effects of NO_2 is uncertainty as to the extent to which NO_2 is the causal agent in giving rise to effects observed in epidemiological studies. The main source of uncertainty in the estimation of the impacts of nitrate in UK air is the toxicity of nitrate relative to other components of PM_{10}. The main source of uncertainty in the estimation of the impacts of ozone is the linkage between UK emissions of NO_2 and total population exposure to ozone arising from these emissions in Western Europe. The main source of uncertainty in assessing the potentiation of PM_{10} impacts by NO_2, is in the limited concentration-response information available.

8.8 DISCUSSION AND CONCLUSIONS

The results of the quantification presented in this chapter suggest that exposure to gaseous NO_2 of anthroprogenic origin in ambient air is associated with an increase in daily death rate and numbers of hospital admissions for cardiovascular or respiratory illness of less than 0.2% and probably less than 0.05%. The increased daily death rate is thought to represent deaths brought forward by weeks rather than years. The effects of NO_2 on respiratory symptoms in the UK may be of more importance than for mortality or hospital admission but there is considerable uncertainty in the concentration-response information.

The UK effects of secondary pollutants arising from UK emissions of NO_x are likely to be relatively small as UK emissions have little impact on UK concentrations of these pollutants. The total impacts of secondary pollutants arising from UK NO_x emissions in Europe are likely to be considerable. The most important secondary pollutant is likely to be ozone. The influence of particulate nitrate is likely to be much smaller than might be estimated from the proportion of nitrate in PM_{10}.

NO_2 may have a substantial impact on the health impacts of particle pollution in the UK leading to a doubling of the number of deaths brought forward associated with PM_{10}. The evidence for an interaction between NO_2 and PM_{10} is, however, weak and actual impacts, if any, are likely to be very much smaller.

9. DISCUSSION

9.1 INTRODUCTION

This chapter draws together various issues raised in the discussion sections of Chapters 3 to 8. The first section of the chapter discusses whether there is sufficient experimental evidence to support the hypothesis that exposure to ambient NO_2 is associated with adverse health effects and the relative importance of exposure during high pollution events versus long term mean levels of exposure. Subsequent sections review the epidemiological evidence linking NO_2 to short and long term effects and discuss the possibility that the effects that have been attributed to NO_2 in epidemiological studies are actually caused by ultrafine particles. The final sections of the chapter discuss the extent to which exposure to NO_2 may potentiate the adverse effects associated with PM_{10} and the potential importance of ambient NO_2 as a cause of ill health within the UK.

9.2 TOXICOLOGICAL EVIDENCE LINKING EXPOSURE TO AMBIENT CONCENTRATIONS OF NITROGEN DIOXIDE TO ADVERSE HEALTH EFFECTS

The results of the toxicological experiments and human volunteer experiments reviewed in chapters 4 and 5 suggest that exposure to concentrations of NO_2 such as arise during high pollution events may have adverse effects on the respiratory health of susceptible individuals. The main effects found at environmentally relevant levels of exposure are evidence of lipid peroxidation and oxidant damage to epithelial lining fluid. This might, in the longer term, contribute to respiratory ill-health, particularly if combined with oxidative damage to the airways associated with inhalation of fine particles or ozone. Effects are greatest in animals with low anti-oxidant status. There is very limited experimental evidence that some asthmatics may develop respiratory symptoms at concentrations equivalent to those found in ambient air during major pollution events. At slightly higher concentrations, NO_2 is associated with a reduced ability to fight infection, enhancement of the allergic response of the airways of asthmatics and increased rates of epithelial cell proliferation. Although these effects are only seen at concentrations exceeding those in ambient air, the general population is likely to include a much wider range of vulnerability than found in groups of laboratory animals or human volunteers. There is very limited evidence to suggest that exposure to NO_2 may contribute to the deposition of material on arterial walls and therefore to circulatory disease.

The effects of NO_2 in animal experiments are related to concentration with peak exposure concentrations being of more importance than longer term mean exposure concentrations. The concentrations required to cause serious lung disease in animals are higher than those typically found in ambient air. In most medium term experiments, the effects of a given dose increase slightly as the duration of exposure increases. There is some evidence of adaptation to NO_2 during longer term exposures at concentrations that are about ten times greater than peak concentrations found in ambient air. In a subchronic experiment with rats, an inflammatory response developed during the first few days of exposure, resolved after a period of weeks. Similarly evidence of oxidative damage to the epithelial lining fluid appears to peak after a few weeks of exposure, suggesting that animals are able to adapt to a given level of oxidative stress. The concentrations at which damage to epithelial cells have been reported are considerably lower than those associated with the progressive resolution of inflammation and there is little evidence that NO_2-induced damage to epithelial cells does not continue on continued exposure to NO_2. It is possible that changes to the epithelial cells are part of the adaptive response to prolonged exposure to NO_2.

There has been very little experimental investigation of the combined effects of NO_2 and nitric oxide despite the co-existence of these pollutants in urban air. Nitric oxide has antioxidant activity but it is unclear how it may modify the oxidative effects of NO_2.

Overall, although ambient concentrations of NO_2 are generally below levels at which measurable effects on the airways have been found in experimental systems, it seems plausible that NO_2 contributes to the cumulative effect of ambient air pollution. Peak exposure concentrations and the variability of exposure concentrations may be of much greater significance than long term cumulative exposure. It seems plausible that the oxidative effects of NO_2 could contribute to a cumulative adverse effect on the epithelial cells. It is probable, however, that the early stages of the process involving modification of the epithelial lining fluid are readily reversible. Antioxidant status may have an important influence on susceptibility.

9.3 EPIDEMIOLOGICAL EVIDENCE FOR AN ASSOCIATION BETWEEN SHORT TERM EXPOSURE TO NO_2 AND HEALTH

9.3.1 Overview

The results of epidemiological studies that have investigated the short term effects of exposure to NO_2 are highly inconsistent (see Chapter 6). Many studies have failed to find statistically significant associations between NO_2 and a range of health endpoints. The evidence of an effect is most convincing for all nonaccidental mortality. This may be partly because it has been the most studied health endpoint, studies include large numbers of cases and there is no ambiguity about the endpoint.

Further uncertainty about the importance of NO_2 has arisen because the apparent effects of NO_2 on health observed in single pollutant models often disappear in multi-pollutant models. There are, however, many studies that do show significant effects and in some of these, the apparent effects of NO_2 do not disappear in multipollutant models. It therefore seems likely that the apparent association between NO_2 and health does reflect something real but there is considerable uncertainty as to whether the effects attributed to NO_2 in epidemiological studies are actually caused by NO_2 or by a co-pollutant with concentrations that co-vary with NO_2.

The results of both animal and human volunteer experiments suggest that peak concentrations and variability in concentrations of NO_2 are likely to be of much greater significance to health than long term mean exposure. Time series analyses have not been specifically designed to assess the relative importance of high pollution events versus day to day variability. There is, however, no epidemiological evidence to suggest that concentration-response functions for ambient NO_2 vary as mean concentrations of NO_2 vary and this would be consistent with the change in concentration being of more importance than the absolute concentrations.

9.3.2 Relevant health endpoints

The results of experiments with animals and human volunteers suggest that an association between high concentrations of NO_2 in ambient air and adverse respiratory effects is plausible. It seems likely that effects would be associated with peak levels of exposure rather than long term mean levels of exposure but there is no way of investigating the “peakedness” of exposure in published studies that have or have not found relationships between NO_2 and health. The association of morning lung function with previous day NO_2 concentrations and lung function later in the day with same day concentrations is consistent with a fairly immediate response to fluctuations in daily mean levels of NO_2 that would be consistent with the findings of volunteer studies.

There is little experimental evidence to suggest that an association between NO_2 and cardiovascular illness is likely, although this could reflect a lack of investigation. A single experimental report has linked NO_2 to phospholipid synthesis in the pulmonary arteries (Li et al, 1994) and a subsequent study found evidence for thickening of the pulmonary arteries at high levels of exposure (Barth et al, 1995). The strength of evidence linking NO_2 to cardiovascular deaths or hospital admissions is, however, similar to that for respiratory illness. This arguably undermines the whole case for an association between ambient concentrations of NO_2 and health. At a recent conference hosted the National Society of Clean Air (Edinburgh, February, 2003), Anthony Seaton strongly expressed his belief that the cardiovascular effects of air pollution are solely due to exposure to ultrafine particles. The inflammatory response of the lung to ultrafine particles is thought to release a range of mediators into the blood stream leading to changes in blood coagulability and heart function that in turn may trigger heart failure in susceptible individuals (Donaldson et al, 2001; Utell and Frampton, 2000). The contribution of NO_2 to any inflammatory response in the lung is likely to be relatively small, although it may contribute to similar circulatory effects to those associated with ultrafine particles. Although, Anthony Seaton thinks the effect would be far too small to be of any relevance (personal communication 2003), it may be premature to completely discount the role of NO_2 in the association between air pollution and cardiovascular ill health.

9.3.3 Confounding by PM_{10}

In many studies concentrations of NO_2 have been strongly correlated with those of PM_{10} or black smoke and this has made the identification of an independent role for NO_2 extremely difficult. Relationships between NO_2 and health have, however, been found where concentrations of NO_2 and PM_{10} are relatively poorly correlated suggesting that the apparent effects of NO_2 are not due to co-exposure to PM_{10}.

9.3.4 Confounding by ultrafine particles

It has also been suggested that NO_2 may be a proxy for some unmeasured component of traffic pollution such as ultrafine particles (eg Wichmann et al, 2000). There are well established relationships between NO_2 and traffic pollution and between traffic pollution and health and it seems likely that concentrations of NO_2 and ultrafine particles would be well correlated in northern and western European cities. In the absence of specific measurements of ultrafine particles (as opposed to $PM_{2.5}$), it is difficult to eliminate the possibility that effects attributed to NO_2 are actually due to ultrafine. Concentrations of NO_2 and ultrafine particles in indoor air are also likely to be strongly correlated and thus exposure to ultrafine particles provides a possible explanation for the health effects associated with gas cooking (Dennekamp et al, 2001). The ratio of concentrations of NO_2 to those of ultrafine particles is likely to be different in indoor air from that in outdoor air and is also likely to vary between different indoor environments depending on the relative influence of outdoor, tobacco smoke and cooking fume sources (section 7.8.1).

The relationship between ambient NO_2 and ultrafine particles is likely to vary in different places and at different times as a result of differing levels of photochemical activity leading to the formation of ozone and other secondary pollutants. The comparison of the results of time series studies undertaken in different places with different levels of traffic pollution and photochemical pollution, did not provide strong evidence that effects attributed to NO_2 are likely to be entirely explicable in terms of exposure to ultrafine particles (section 6.12.6). In theory, it should be possible to design a study that compared the relationships between NO_2 or ultrafine and a health endpoint like daily mortality in cities with very different ratios of NO_2 to ultrafine particles in order to determine the relative importance of each pollutant. In practice is would be difficult to select cities with directly comparable populations and to

exclude confounding factors such as differences in smoking habits. Panel studies in which exposures to NO_2 and ultrafine could be measured or modelled for individuals could provide a useful mechanism for looking at relationships between NO_2 or ultrafine and a range of measures of respiratory and cardiac health.

9.3.5 Factors influencing the size of the apparent effect of NO_2

The failure of epidemiological studies to consistently detect an association between NO_2 and health may be a reflection of the relatively small size of any effect and the poor correlation between ambient and personal exposure concentrations. It seems likely that the health impacts of short term exposure to NO_2 are of much less importance than those associated with particles. There are several factors that may contribute to the relatively small scale of effects. Firstly, there is limited evidence from experimental studies and case reports that individuals can adapt to a given level of NO_2 exposure such that only major changes in concentration are likely to give rise to adverse effects. Secondly, smokers are exposed to vastly more NO_2 in cigarette smoke than they inhale in ambient air such that the NO_2 that they inhale in ambient air may be virtually irrelevant to the development of adverse effects. This means that population effects are likely to be concentrated in nonsmokers but averaged across the whole population, thereby greatly reducing the apparent size of any effect. Thirdly inhaled NO_2 reacts with the lung lining fluid and is effectively "neutralised" on contact whereas particles would persist for hours to days within the lung and would therefore be capable of stimulating a much more prolonged cellular response. Fourthly NO_2 is a relatively weak oxidant that can be absorbed by antioxidants within lung lining fluid whereas the oxidant burst arising from the cellular reaction to particles is less likely to be moped up by these antioxidants and more likely to lead to a systemic response.

9.3.6 Conclusions

Overall, it seems likely that exposure to NO_2 during high pollution events does adversely affect the health of a susceptible minority among the population. A proportion of the observed effects may, however, arise from concurrent exposure to particles, particularly ultrafine particles, rather than as result of exposure to NO_2. There is insufficient evidence at present to allow the apparent effects of NO_2 to be entirely attributed to ultrafine particles.

9.4 EVIDENCE FOR AN ASSOCIATION BETWEEN LONG TERM EXPOSURE TO NO_2 AND HEALTH

The results of experimental studies suggest that variability in concentrations of NO_2, and particularly the number and frequency of high pollution events, is likely to have a more important influence on health than long term mean concentrations. Adverse effects on airways epithelial cells in long term experiments have only been reported at concentrations equivalent to ten times peak ambient concentrations and early signs of inflammation resolve on prolonged exposure to even higher concentrations of NO_2. There is some evidence of oxidative damage at lower levels of exposure (2-3 times ambient) but no evidence that this progresses to more serious effects. There is also both experimental and limited epidemiological and case-report information that suggests that individuals can adapt to a given level of exposure to NO_2.

The results of epidemiological studies of the effects of long term exposure to nitrogen dioxide are not strongly suggestive of adverse effects. There is a much less consistent association between NO_2 and mortality than has been reported for particles. The results of a number of studies suggest that NO_2 may adversely affect respiratory health, particularly symptoms such as cough and wheeze and some measures of lung function. The apparent effects on symptoms can be substantial, but the results of individual studies are highly inconsistent, both in the

symptoms associated with NO_2 and in the scale of effects. Reported effects on lung function are generally small. Given the association between lung function and life expectancy, it would seem possible that exposure to NO_2 may have a very small adverse effect on life expectancy. It also seems plausible that exposure to NO_2 may contribute to the development of chronic respiratory disease, particularly if exposure is combined with exposure to other pollutants such as PM_{10} and O_3 that are associated with oxidative activity. In contrast, with the time series studies, there are no reported cardiovascular effects, which, although the data are limited, may indicate that NO_2 is not a simple proxy for ultrafine. There are insufficient high quality studies to allow the selection of reliable concentration-response functions for quantification.

The difficulties with the identification of the long term effects of NO_2 in epidemiological studies include the poor correlation between personal exposure concentrations of NO_2 and concentrations measured at central monitoring sites and the presence of a high proportion of smokers in the population. Smokers are exposed to more NO_2 in cigarette smoke than is present in ambient air and those living, working or socialising with smokers are likely to be exposed to substantial quantities of NO_2 in environmental tobacco smoke. These factors are likely to have weakened the power of epidemiological studies to detect effects. Other studies have considered only indoor air quality and have relied on gas cooking as an index of exposure. The WHO (1997) meta-analysis of the effects of NO_2 on the respiratory health of children, for example, actually demonstrates an association with gas cooking rather than with NO_2. The studies reviewed in Chapter 3 demonstrated that gas cooking accounts for less than half the variability of mean personal exposure concentrations and that the indoor air quality impacts of gas cookers vary greatly between properties.

Another factor that has weakened the power of epidemiological investigations to detect adverse effects associated with NO_2, is that concentrations of NO_2 tend to be well correlated with those of particles in both time and space. It is therefore difficult to attribute effects unambiguously to NO_2. Future investigations that measure and /or model personal exposure concentrations for NO_2 could play an important role in improving understanding of the influence of long term exposure to NO_2 on health, particularly if studies recruited nonsmokers rather than examining a more representative sample of the population.

Overall, it seems unlikely that long term exposure to NO_2 has a substantial effect on health, and any impacts are likely to be much smaller than those for particles. The failure of epidemiological studies to consistently detect an association between NO_2 and health would be consistent with any effect being very small. It would be premature to state that long term exposure to ambient concentrations of NO_2 in the UK has no adverse effect on health. It seems likely that effects are more strongly associated with the number and frequency of high pollution events and although these measures will be correlated with long term concentrations, the relationship is likely to vary in different places.

9.5 VULNERABLE GROUPS

The results of many time series studies have suggested that both the elderly and children are more susceptible to the effects of NO_2 and other air pollutants than adults of working age (Chapter 6). Zmirou et al (1996), for example, demonstrated that the average age of those who died on high pollution days was greater than of those who died on other days. With NO_2, the apparently stronger associations between NO_2 and a range of health endpoints for these groups, could be partly or wholly due to the stronger correlation between personal exposure and ambient concentrations than for adults of working age (section 6.12.2 and 6.12.4). It is also likely that the effects of tobacco smoke in obscuring the potential relationship between NO_2 and health would be smaller for these groups (section 6.12.2). A further factor that may influence increased GP consultation and hospital admissions for these groups is differences in

medical practice with respect to different age groups. Parental concern may lead to increased rates of GP consultation and emergency hospital visits for children, giving rise to greater apparent effects than for older age groups. There is experimental evidence, however, that indicates that young weaned animals and old animals are more susceptible to the effects of NO_2 than mature animals of intermediate age (WHO, 1997). This provides limited further evidence to suggest that the young and the old are more susceptible to the adverse effects of NO_2 than adults of working age.

There is limited experimental evidence that suggests asthmatics are likely to be more susceptible to the adverse effects of NO_2 than other individuals (WHO, 1997). Few epidemiological studies have specifically investigated the relative susceptibility of asthmatics and nonasthmatics. Boezen et al (1999) found a stronger association between NO_2 and upper respiratory symptoms in children with raised IgE and bronchial hyper-responsiveness than in other children, but the significance of this finding is unclear as the reverse was found for lower respiratory symptoms. Roemer et al (1999) found no evidence that children with chronic cough, atopy or asthma were more susceptible to the effects of air pollution than other children.

There is limited epidemiological evidence to suggest that individuals with pre-existing illnesses are more susceptible to the adverse effects of air pollution than healthy individuals (eg Kwon et al, 2001). In addition, there is limited evidence to suggest that the elevated mortality rates during high pollution events are linked to lower rates of mortality during subsequent weeks (Campbell and Tobias, 2000). This would be consistent with mortality effects being concentrated among those who were seriously ill with a life expectancy of only a few weeks.

There is limited experimental evidence to suggest that individuals with low antioxidant status are likely to be more susceptible to the adverse effects of NO_2 than others in the population (Chapter 5). This implies that diet may play an important role in governing susceptibility to NO_2 and other air pollutants.

9.6 EFFECT OF NO_2 ON THE ASSOCIATION BETWEEN PARTICLES AND HEALTH

There is very limited toxicological information to suggest that NO_2 may enhance the adverse effects of particles. There is also experimental evidence that suggests that the effects of ultrafine particles are significantly enhanced by gaseous pollutants such as ozone (Oberdorster, 2001). Although NO_2 is a weaker oxidant than ozone, it seems plausible that it would also similarly increase the oxidative stress associated with inhaled particles. Absorption of NO_2 by lung lining fluid is likely to contribute to the consumption of antioxidants and thereby reduce the extent to which the reactive oxygen species generated during the cellular response to particles can be moped up. The results of the APHEA 2 epidemiological study strongly suggest that the adverse effects of particle pollution are enhanced at high concentrations of NO_2. The APHEA 2 study involved cities across Europe and the results are convincing. There is very limited evidence from the collected results of all the studies of respiratory mortality reviewed in Chapter 6 of a more general relationship between the concentration-response function for PM_{10} and concentrations of NO_2. No such relationships were apparent for all-cause or cardiovascular mortality. The apparent concentration-response function linking PM_{10} to acute mortality in US cities with low NO_2 concentrations was steeper than that found in cities with higher NO_2 concentrations (Samet et al, 2000). There is little epidemiological evidence that concentration-response relationships linking PM_{10} to other health endpoints are affected by NO_2 concentrations. Spix et al (1998) report limited evidence that suggests the association between respiratory hospital admissions and black smoke in European cities is stronger at high concentrations of NO_2, but similar

effects have not been reported by other studies and are not apparent in cross study comparisons. There is also no epidemiological evidence that concentration-response relationships for NO_2 are affected by PM_{10} concentrations.

A possible explanation for the findings of APHEA 2 and the earlier findings of Spix et al, is that NO_2 is acting a proxy for traffic pollution more generally and high levels of NO_2 are associated with a high proportion of traffic derived particles in PM_{10}. The apparent relationship with NO_2 may arise because in cities with high concentrations of NO_2, there is a greater proportion of combustion generated ultrafine particles in PM_{10} and that PM_{10} during periods of elevated concentrations of traffic pollution is more biologically active at other times. The absence of a more general relationship between concentrations of NO_2 and concentration-response functions for PM_{10} may partly reflect the large variability between studies that limits comparison across studies. It is also possible that photochemical activity in North America has led to a weaker association between NO_2 and the proportion of ultrafine in PM_{10}. The vehicle mix and fuel use by stationary sources in North America is also likely to differ from that in Europe and emissions of NO_x and ultrafine may be less strongly correlated than in Europe. Given the fairly well established link between ultrafine particles and cardiovascular illness, the apparent association of NO_2 enhancement of particle effects with respiratory rather than cardiovascular illness may, however, provide limited evidence that the effect is due to gaseous NO_2 rather than ultrafine particles.

Overall, although an interaction between NO_2 and particles seems plausible, it is not proven. The evidence appears to be strongest for serious respiratory illness. There is also insufficient evidence to be certain that, where an apparent interaction between NO_2 and particles has been found, the effect is due to NO_2 and not explicable in terms of NO_2 acting as an index of ultrafine particle levels.

9.7 SCALE OF HEALTH IMPACTS ASSOCIATED WITH NO_2 IN THE UK

9.7.1 Direct impacts

The results of the quantification undertaken in this study are highly uncertain because the effects of gaseous NO_2 are indistinguishable from those of other components of traffic pollution in epidemiological studies. The concentration-response functions used in the quantification are therefore likely to represent the effects of traffic pollution as assessed from levels of NO_2 rather than the direct effects of gaseous NO_2. It seems likely that gaseous NO_2 contributes something to these traffic pollution effects such that there is some validity in using the concentration-response functions to estimate the potential impact of NO_2. It is not clear, however, whether the relative contribution of NO_2 to the health effects associated with the mix of traffic generated pollutants is the same across the spectrum of NO_2 concentrations found in ambient air. If the effects of NO_2 are only important above some currently unspecified threshold, then the available concentration-response functions would give a very inaccurate picture of potential effects. In addition to the considerable uncertainty in the concentration-response information available, there is also uncertainty in the baseline rates for health endpoints other than mortality and emergency hospital admission. There is therefore a particularly high level of uncertainty in the quantification of the use of primary healthcare facilities, symptoms and restricted activity days.

The upper bound estimates of effects presented in Chapter 8 are based on reported concentration-response functions for NO_2, but may be more indicative of the potential impacts of traffic pollution rather than the direct effects of gaseous NO_2. The impacts of gaseous NO_2 may only be 10% of those estimated using the available concentration-response function (lower bound estimates in Chapter 8). Given that the upper bound estimates may reflect the effects of traffic pollution rather than the direct effects NO_2, it is unclear whether these

estimated effects are truly additional to those calculated for PM_{10} or whether there is an element of double counting. There is very limited evidence to suggest that the effects of ultrafine particles are not fully accounted for by concentration-response functions derived for PM_{10} in epidemiological studies (Wichmann et al, 2000). If NO_2 is acting as a marker for ultrafine, then at least some of the calculated apparent effects for NO_2 are likely to be truly additional to those calculated for PM_{10}.

The uncertainties in the quantification of effects arising from exposure to NO_2 in the UK may be relatively unimportant as the estimated effects are much smaller than those likely to arise from exposure to PM_{10}. This is mainly because of the substantial effects of PM_{10} on long term life expectancy (see Searl et al, 2003). The results of the quantification presented in Chapter 8 suggest that exposure to ambient NO_2 of anthroprogenic origin is associated with an increase in daily death rate and numbers of hospital admissions for cardiovascular and respiratory illness of less than 0.2% and probably less than 0.05%. The increased daily death rate represents deaths brought forward by days or weeks rather than years. The effects on the number of GP consultations for respiratory illness and the prevalence of respiratory symptoms in the UK population may be greater than for daily death rate or hospital admission. Asthmatics in the UK population may experience between 7.3 and 73 million days of respiratory symptoms per annum as a result of exposure to NO_2. This is equivalent to between 1 and 7 days/asthmatic/year. More generally the UK population may experience between 1.5 and 15 million restricted activity days as a result of acute respiratory illness associated with exposure to NO_2. This could represent a substantial effect with respect to sickness absence and increased care costs. The effects on long term illness and life expectancy are impossible to quantify with any certainty, but are likely to be much smaller than the effects associated with particles. Concentrations of NO_2 and, therefore, associated health effects have fallen substantially since 1990 and are likely to fall further before 2010 (DETR et al, 2000). Beyond 2010, only a small reduction in total NO_2 concentrations arising from anthroprogenic activities in the UK and Europe is likely to arise from further emissions management beyond the measures that are currently in place.

In conclusion, the apparent health impacts of NO_2 in the UK population may be substantial including between 1400 and 14000 hospital admissions and millions of lost working days. The actual effects of gaseous NO_2 are likely to be very much smaller than the apparent effects and of less importance than those of particles. This is largely because of the absence of proven effects on life expectancy. If the apparent effects of NO_2 are largely due to some other component of traffic pollution, then the estimated apparent effects of NO_2 give some indication of the overall impact of traffic pollution. It is unclear, however, to what extent the implied impact of traffic pollution would be truly additional to any separately calculated impact of PM_{10}.

9.7.2 Scale of health impacts associated with secondary pollutants arising from NO_X emissions

UK emissions of NO_x have a fairly small influence on UK concentrations of ozone, nitrate and nitrous and nitric acids and the health impacts of secondary pollutants arising from UK emissions are likely to be much greater in mainland Europe. If transboundary pollution from Europe is included in the assessment of the importance of secondary products of NO_x emissions, then the health impact of these species is potentially substantial in comparison to the impact of NO_2.

The secondary pollutant of most importance of health is ozone and the effects of ozone may be greater than of NO_2. The health impacts of current levels of ozone in the UK are uncertain, partly because it is unclear whether a threshold exists in the concentration-response information.

Secondary nitrate particles contribute about 10% of the mass of PM_{10} in the UK, but probably less than 5% of the health impact of PM_{10}. Experiments in humans with airborne nitrate salts have failed to demonstrate adverse effects at concentrations that are two orders of magnitude greater than those found in ambient air (WHO, 1997). Nitrate particles would be expected to have a limited lifetime in the airways because of their solubility and would not be expected to induce the normal reaction to inhaled particles.

There is limited evidence to suggest nitrous and nitric acid may have a small influence on respiratory health. Levels of aerosol acidity have fallen substantially in recent years following reductions in sulphur dioxide emissions. The impact of nitrous and nitric acid on health is likely to be small in comparison with that of NO_2.

9.7.3 Scale of health impacts arising from the interaction of NO_2 and PM_{10}

The results of the quantification of daily mortality effects arising from PM_{10} using concentration-response functions for PM_{10} and NO_2 derived from Katsouyani et al (2001) suggest that ambient concentrations of NO_2 in the UK may increase the effects of PM_{10} on mortality by a factor of two. Given, however, that the results of other studies are not consistent with the findings of Katsouyani et al (section 6.2.8), it seems likely that this is a vast over-estimation of the influence of gaseous NO_2 on particle-induced effects. It seems plausible, however, that NO_2 may slightly enhance the effects of PM_{10} during high pollution events, although the magnitude of the effect may only be 10% of that estimated using the concentration-response relationships reported by Katsouyani et al.

9.8 GAPS IN KNOWLEDGE

The most important uncertainty in assessing the health impacts associated with NO_2 is the separation of the effects of NO_2 from those of ultrafine particles and of particles more generally. This could addressed by experimental studies that investigated the relative levels of oxidative stress, inflammation and enhancement of allergic response associated with ultrafine particles and with NO_2 and with combinations of the two pollutants. It may be difficult, however, to design exposure systems for animals or human volunteers that can reliably deliver uniform ultrafine aerosols in combination with controlled concentrations of NO_2. Ideally epidemiological studies could also be conducted that linked personal exposure and ambient concentrations of NO_2 and ultrafine particles to appropriate health endpoints such as lung function and respiratory symptoms that can be readily assessed in panel studies. The selection of an appropriate study population would need to consider whether the likely variation in concentrations of ultrafine and NO_2 would be sufficient to allow separation of the effects of each pollutant. The study should also be designed to allow separation of the effects of age from those of differences of exposure and to allow comparison of asthmatics and nonasthmatics. The biggest problems in conducting an epidemiological study would be in the recruitment of a large enough number of individuals to participate in the study and also in the measurement of their personal exposure. The modelling of individual exposures based on some simple questionnaire questions may be a more realistic approach that would yield information of almost comparable certainty. Another approach might be to conduct time-series studies in cities in which concentrations of ultrafine and NO_2 are relatively poorly correlated because of the presence of NO_2 sources or sinks other than traffic pollution.

Other uncertainties about the health impacts of NO_2 include the effects of interaction with airborne particles and with NO. There is very little experimental data about the combined effects of NO_2 and particles or the combined effects of NO_2 and NO. Although there have been many investigations of the effects of tobacco smoke, the role of NO_2 in enhancing the toxic effects of tobacco smoke have not been specifically investigated. It seems plausible that NO_2 would amplify any particle effects but that NO might substantially reduce effects

associated with NO_2. There is also little epidemiological information about the effects of NO_2 on response to airborne allergens despite the results of a number of experimental studies that have suggested such effects may be important in asthmatics (Chapter 5).

Experimental studies suggest that variability of NO_2 concentrations may be more important than long term mean exposure. Epidemiological investigations have not specifically investigated whether adverse effects are more strongly associated with changes in NO_2 concentration than with mean concentrations. There is a need to determine whether the adverse effects of NO_2 are more strongly associated with high pollution events than with smaller day to day variability and whether concentration-response functions become steeper as the change in concentrations becomes greater. It is also unclear whether any long term effects of NO_2 might be more strongly associated with the number and frequency of high pollution events than with mean concentrations.

Epidemiological studies suggest that there may be some variability in susceptibility to the adverse effects of NO_2, but it is unclear to what extent this is due to differences in susceptibility or differences in exposure estimation. Studies in which personal exposure concentrations are measured or estimated could play an important role in separating age effects from exposure effects.

10. SUMMARY OF FINDINGS AND CONCLUSIONS

10.1 EXPOSURE

Personal exposures to concentrations of NO_2 are only weakly correlated with ambient concentrations measured at central locations. Gas cooking, environmental tobacco smoke, smoking and proximity to major traffic routes are major influences on personal exposures to NO_2.

Sources of NO_2 in both the general environment and indoors are also sources of ultrafine particles and concentrations of these pollutants are likely to be well correlated.

10.2 EXPERIMENTAL STUDIES

Experiments with animals and human volunteers have identified minor respiratory changes at concentrations of NO_2 similar to those arising during high pollution events.

The experimental results also suggest that exposure to NO_2 during high pollution events is likely to have a greater adverse impact on health than long term exposure to lower concentrations.

There is limited evidence to suggest adaptation of both humans and animals to NO_2 on prolonged or repeated exposure, particularly with respect to inflammation. Other health endpoints such as increased rates of endothelial cell proliferation do not resolve on continued exposure, but are only found at concentrations of NO_2 that greatly exceed those in ambient air.

Experimental evidence to link NO_2 to adverse cardiovascular effects is extremely limited.

10.3 EPIDEMIOLOGICAL STUDIES

The power of epidemiological studies to detect the effects of NO_2 is weakened by the relatively poor correlation between personal exposure concentrations of NO_2 and ambient concentrations measured at central monitoring sites. The power of studies of the general population is also weakened by the large numbers of smokers as their exposure to NO_2 in ambient air is tiny in comparison with that in tobacco smoke.

The results of time-series studies suggest that NO_2 has a small effect on daily mortality, hospital admission for respiratory and cardiovascular illness, emergency hospital and GP visits for respiratory illness and lung function. Effects are small in comparison to those of particles, but are found both in studies where concentrations of NO_2 and particles are well correlated and in studies where these pollutants are poorly correlated.

The association of NO_2 with cardiovascular illness is arguably indicative that the apparent effects of NO_2 are actually due to confounding by ultrafine particles, although it is difficult to exclude the possibility that NO_2 contributes to cardiovascular effects through the generation of an inflammatory response within the lung.

It is unlikely that the apparent association between ambient NO_2 and health is entirely due to some unmeasured co-pollutant, such as ultrafine particles, that is present in both traffic fumes and cooking fumes. Ultrafine particles may, however, account for some of the apparent effects of NO_2.

The effects of long term exposure to NO_2 appear to be small and are certainly much smaller than those associated with particles. It was not possible to select a suitable concentration-response function for the quantification of effects.

10.4 INTERACTION OF NO_2 AND PARTICLES

There is limited evidence to suggest that exposure to NO_2 may potentiate the effects of PM_{10} on health. Both pollutants are associated with oxidative damage to the airways lining fluid and thus it seems plausible that their combined effects would be greater than for PM_{10} alone. There is currently uncertainty as to the reliability of the single concentration-response function for PM_{10} that incorporates NO_2 for quantification of effects. It is possible, that the variation in the apparent effects of PM_{10} in the source study was due to variability in the proportion of PM_{10} derived from traffic fumes, rather than an effect of co-exposure to NO_2.

10.5 QUANTIFICATION OF EFFECTS

It is difficult to fully quantify the short and long term impacts of NO_2 pollution because of uncertainties in the concentration-response functions available. These uncertainties arise because concentrations of NO_2 and PM_{10} are often strongly correlated in space and time and this has limited the power of epidemiological studies to reliably attribute effects to NO_2.

A preliminary estimate of the direct effects of NO_2 on the health of the UK population suggests that between 600 and 6000 deaths per year may be brought forward by days or weeks as a result of exposure to NO_2 in ambient air. Similarly, between 1400 and 14000 hospital admissions, and between 200000 and 2 million GP consultations for respiratory illness may arise each year as a result of exposure to ambient NO_2 in the UK. Ambient NO_2 may contribute to an average of between 1 and 7 extra days of symptoms in asthmatics each year, and more generally, individuals may experience an average of between 0.03 and 0.3 restricted activity days due to respiratory illness each year. It seems likely that the actual impacts of NO_2 itself are towards the lower end of the estimated ranges given.

The effects of long term exposure to NO_2 in the UK are unclear but are likely to be very much smaller than for particles.

The indirect effects of NO_x emissions on health arising from the formation of ozone, nitric acid and nitrate particles may be substantial in relation to direct impacts of NO_2. The indirect impacts of NO_x emissions from the UK dominantly arise in mainland Europe and similarly the impacts of ozone, nitric acid and nitrates in the UK are largely associated with primary emissions from mainland Europe.

The indirect effect of NO_2 on the health impacts of PM_{10} in the UK could be substantial. The application of concentration-response information from a single European study suggests that the potentiation of the effects of PM_{10} by NO_2 could lead to an extra 40 000 deaths a year being brought forward. There is considerable uncertainty as to the reliability of the concentration-response function, however, as other studies have not found a similar interaction between NO_2 and particles.

10.6 CONCLUSIONS

The health impacts of ambient NO_2 are likely to be of minor importance compared with those of PM_{10}. Although the simple application of concentration-response functions suggests that the apparent impacts of NO_2 on health in the UK are substantial, it seems unlikely that the effects attributed to NO_2 in the source epidemiological studies were caused solely by NO_2. A substantial component of the apparent health impacts of ambient NO_2 could be largely due to

exposure to some other component of traffic pollution such as ultrafine particles. The influence of NO_2 on health is likely to be greatest during high pollution events and NO_2 may contribute little to the adverse effects associated with long term exposure to air pollution. The indirect effects of UK emissions of NO_x on health within the UK and elsewhere in Europe, are highly uncertain, but could be substantial. Indirect effects include those associated with ozone, enhanced particle concentrations and the enhancement of particle toxicity.

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Institute of Occupational Medicine

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Applying science for a better working environment

The Institute of Occupational Medicine

The IOM is a major independent centre of scientific excellence in the fields of occupational and environmental health, hygiene and safety. We aim to provide quality research, consultancy and training to help to ensure that people's health is not damaged by conditions at work or in the environment. Our principal research disciplines are exposure assessment, epidemiology, toxicology, ergonomics and behavioural and social sciences, with a strong focus on multi-disciplinary approaches to problem solving.

Our beginnings

Our first major research programme began in the 1950s, on respiratory health problems in the coal mining industry. Major themes were quantification of airborne dust concentrations in different jobs, characterisation of types and constituents of the dusts, measurement of health effects, relationships between exposure and disease, and proposals for prevention. This research became an international benchmark for epidemiological studies of occupational health, and was the primary influence on dust standards in mines in the UK, US and other countries.

Current themes

Our current work spans many other industries including asbestos, MMMF, pesticides, chemicals, energy, telecoms, metals, textiles, construction, agriculture as well as the environment. While diseases of the respiratory tract remain a major interest, our scope now extends to many other health outcomes such as mortality, cardiovascular effects, cancer, back pain, upper-limb disorders, hearing loss, skin diseases, thermal stress and psychological stress. Related work includes the development and application of measurement and control systems, mathematical models and survey methods.

Who we work for

Our work in these areas is conducted for a wide range of organisations in the UK, the EU, and the US, including Government departments, international agencies, industry associations, local authorities, charitable organisations, and industrial and commercial companies. The IOM is a World Heath Organisation (WHO) collaborating centre and is an approved institute of the Universities of Edinburgh and Aberdeen, enjoying collaborative research links with NIOSH, IARC, and many other institutes throughout the world.

Publication

We believe that our research findings should be publicly available and subject to the scrutiny of the international scientific community. We publish our findings in the peer reviewed scientific literature and through our own series of Research Reports.

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