Health effects of exposures to mixtures of air pollutants / Advisory Group on the Medical Aspect of Air Pollution Episodes.

DEPARTMENT OF HEALTH

Advisory Group on the Medical Aspects of Air Pollution Episodes

FOURTH REPORT

HEALTH EFFECTS OF EXPOSURES TO MIXTURES OF AIR POLLUTANTS

HMSO

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Chairman: Professor Anne Tattersfield

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Foreword by the Chief Medical Officer

The publication of this report, the fourth by the Advisory Group on Medical Aspects of Air Pollution Episodes (MAAPE), marks the completion of the work of this Group. Each of the previous reports has provided expert, balanced opinions which have contributed to the development of policy in the field of air pollution.

In tackling the complex problem of the health effects likely to arise from exposure to mixtures of air pollutants during episodes occurring in the United Kingdom the Advisory Group has built on the work which it began in 1990. The difficulties encountered in assessing the published work in this area are made clear in this report, which matches up to the high standards of its predecessors.

The recognition that the influence of air pollutants on health may occur at any time, not just during an episode, has led to the formation of the Committee on the Medical Effects of Air Pollutants (COMEAP) with a more general remit than MAAPE. With many members of MAAPE now serving on COMEAP, the Department of Health looks forward to receiving continued advice of excellent quality.

I am grateful for the work of the Advisory Group and give my thanks to all the members who have contributed to the four reports of the Group.

K C Calman

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We also thank the authors and publishers who have given permission for the following illustrations to be used:
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Chapter 1

Executive Summary

1.1 The Advisory Group on the Medical Aspects of Air Pollution Episodes was set up to provide advice to the Chief Medical Officer in accordance with the Terms of Reference:

> To consider whether advice about personal protective measures during air pollution episodes should be given by Central Government and, if so, what that advice should be, to whom it should be addressed, and the criteria which should be adopted for the issuing of any advice.

1.2 The Advisory Group was asked to consider the effects of exposure to air pollution episodes in which the concentration of more than one pollutant was raised above background levels. In the Advisory Group's previous reports the individual air pollutants have been considered separately.

1.3 Predicting the effects of exposure to combinations of pollutants proved to be difficult. The Advisory Group therefore recommends caution when considering the effects of exposure to more than one pollutant and points out that the level of understanding of the mechanisms of possible interactive effects is even less well developed than the understanding of the mechanisms underlying the health effects of individual pollutants.

1.4 The Advisory Group identified three common types of air pollution episode:

- Type 1: Summer smog, the pollution mixture with the main, or indicator, pollutant being ozone;
- Type 2: Vehicle smog, the indicator pollutant being oxides of nitrogen;
- Type 3: Winter smog, the indicator pollutant being sulphur dioxide, with a contribution from oxides of nitrogen.

Elevated concentrations of particles may occur during all three types of air pollution episode.

1.5 A main concern in this report has been the question of whether the biological effects of mixtures of air pollutants differ from those of the individual pollutants in isolation. Potentiation of damage (synergism) has been seen following exposure of animals to some combinations of pollutants. However, there is a paucity of information on the toxicological effects of complex mixtures of pollutants, particularly those that relate to the three main types of pollution episode seen in the United Kingdom.

1.6 Pollen and fungal spores, or their fragments, are common aeroallergens during the period between the late spring and the early autumn. They are responsible for attacks of hay fever or deterioration in asthma in sensitised individuals. Elevated aeroallergen levels may occur in conjunction with Type 1 air pollution episodes. A limited number of laboratory studies, in which human subjects have been exposed to relatively high concentrations of air pollutants, have demonstrated an enhanced reaction to aeroallergens.

1.7 In laboratory studies of human subjects exposed to combinations of air pollutants the results have been variable. There has been no clear evidence of synergism between pollutants at the concentrations studied, although interactions between air pollutants may have been underestimated in such studies due to the small size of many studies, limited durations of exposure and the confounding effects of prior exposure to ambient pollutants.

1.8 It is probable that all three main types of pollution mixtures encountered during air pollution episodes in the United Kingdom could cause small mean reductions in lung function in normal individuals. The evidence for this is probably strongest for ozone-related pollution, where reduction in lung function and development of symptoms is more likely in those who exercise. There is no evidence that any of the three types of episode commonly seen in the United Kingdom cause symptoms or adverse health effects in people who are otherwise well.

1.9 It is likely that episodes of air pollution occurring in the United Kingdom produce adverse health effects in some persons with chronic respiratory disease. There is also evidence that some individuals with asthma might experience some deterioration in their condition, although the majority have shown little effect in most studies.

1.10 The elderly, especially those with chronic cardiopulmonary disorders, are identified as being at increased risk of deterioration during air pollution episodes. The degree of increased risk incurred by these groups is difficult to quantify.

1.11 It might be expected that patients with asthma would be especially vulnerable to air pollution. At levels encountered in the United Kingdom this has proved difficult to demonstrate convincingly, except possibly in those with severe asthma. It is possible that asthmatic patients might compensate for any effects of air pollutants by increasing their medication.

1.12 Evidence relating to the long term health effects of exposure to such episodes of air pollution as occur now in the United Kingdom is not available.

1.13 It is recommended that information on air pollution episodes continue to be provided to the public. More detailed information about the type of air pollution episode expected, the indicator pollutant and any associated pollutants, geographical location, severity and its likely duration should be provided in forecasts.

1.14 It is recommended that the banding system nomenclature suggested in previous reports of the Advisory Group be adopted and applied to episodes of air pollution in which levels of pollutants are elevated. If it were to be predicted that the concentration of a pollutant would pass into the **"Very Poor"** band then the episode should be characterised as **"Severe"**.

1.15 The Advisory Group identified criteria that needed to be fulfilled if health advice provided to the public is to be beneficial. These included: the ability to predict an episode sufficiently far in advance, the ability to target advice to groups at risk, and the existence of effective interventions for those at risk.

1.16 It was recognised that the identification of groups at risk and the understanding of effective interventions for such groups were each subject to some uncertainty. The Advisory Group therefore recommended that this topic be kept under review by the Committee on the Medical Effects of Air Pollutants.

1.17 The Advisory Group considered the medical advice which should be provided during air pollution episodes and recommended that the following text should be used on the FREEPHONE Air Quality Helpline:

> 'The following advice on health applies only on days when air quality is **"Poor"** or **"Very Poor"**. If you have a chest problem, such as asthma or bronchitis, you may experience a worsening of your symptoms on these days. If this is the case it might help to increase your treatment temporarily – you should talk to your doctor about the options.'

1.18 The use of smog masks during air pollution episodes is not recommended on current evidence.

1.19 It is recommended that the findings of this report be drawn to the attention of doctors.

1.20 A number of recommendations for further research are made; these are detailed in Appendix 1.

Chapter 2

Introduction

2.1 The present series of reports is concerned with the effects on health of episodes of elevated concentrations of air pollutants. The Advisory Group looked first at the effects of exposure to specific compounds – ozone,[1] oxides of nitrogen,[2] and the complex of closely related pollutants: sulphur dioxide, acid aerosols and particulates.[3] Depending on season, meteorological factors and source strengths, different components are dominant in particular episodes: ozone is important in episodes occurring in hot sunny weather in the summer; sulphur dioxide and acid aerosols feature more in episodes occurring in calm cold conditions in the winter (particularly in coal-burning communities); while episodes involving nitrogen dioxide and particles are liable to arise in any season.

2.2 In each type of episode, however, several pollutants may be increased and the population is exposed to a complex pollutant mixture. This final report in the series considers information available on the composition, properties and response to the types of mixtures found in the United Kingdom, with the emphasis on urban areas where emissions are greatest. The sources of air pollutants have changed greatly over the past few decades as the use of coal for domestic heating has diminished and virtually disappeared in major towns; at the same time the greatly increased number of motor vehicles, and the consequent greater congestion on the roads, has led to increased emissions from that source. The net result has been substantial reductions in many pollutants but an increase in complexity of the pollution mixture.

2.3 What constitutes an episode of elevated air pollution is to some extent arbitrary and the criteria have changed over the years. In the aftermath of the 1952 smog episode in London one definition[4] was a 24-hour average concentration of either black smoke or sulphur dioxide exceeding 1000 $\mu g/m^3$ for at least two successive days; the question of issuing health warnings via radio or television was considered when the hourly mean concentration of sulphur dioxide reached 2000 $\mu g/m^3$ (700 ppb). Now, criteria depend on a wider range of pollutants including nitrogen dioxide and, in summer, ozone, whilst any "trigger" in respect of sulphur dioxide is at a much lower concentration than that used in the 1950s. Such changes reflect the higher expectations today in respect of air quality, the recognition of a wider range of adverse effects on health in response to inhaled pollutants and the total impact of the more complex mixture.

2.4 To investigate the effect of real mixtures as they occur in episodes reliance has to be placed mainly on epidemiological studies. Because concentrations of several pollutants tend to rise together, it is often difficult to determine whether the health effects observed relate more to one pollutant than to another or whether they represent additive or synergistic effects of components of the mixture. The health effects may include an increase in deaths, hospital admissions or general practitioner consultations and, in some studies, changes in lung function. One large data set that has been analysed and re-analysed many times to determine the respective rôles of sulphur dioxide and black smoke comprises day-to-day variations of mortality in London in the 1950s and 1960s. Associations have been demonstrated with the secondary acid aerosol as well as with the primary pollutants,[5] but it is likely that the complete mixture was involved, with the different components all playing some part. Re-analysis using sensitive and recently developed statistical techniques have demonstrated that health effects may have occurred at levels of pollution originally regarded as unlikely to be harmful. Further information is emerging now as episodes involving different mixtures arise, and findings from one that occurred in London in 1991 in which nitrogen dioxide was a notable component[6] are considered in detail in the present report.

2.5 There are a number of ways in which pollutants may interact. Chemical reactions

can occur in the air or in the course of inhalation, enhancing or reducing the effects of the individual pollutants. Different components of pollution mixtures may deposit in different parts of the respiratory tract, producing separate types of effect. The pathological effects of one pollutant may potentiate those of another, and whether they are inhaled in sequence or simultaneously may affect the outcome. These aspects have been explored in a wide range of animal and human inhalation studies, using mixtures of two or three specific pollutants, such as sulphur dioxide with ozone or nitrogen dioxide and, to a limited extent, polluted urban air. As in the case of controlled human exposures to single pollutants, intra-subject variations in human response are substantial, accentuating the difficulties of interpreting the results of experiments.

2.6 A further aspect of combined effects of different agents in the environment concerns interactions between pollutants and pollens or other aeroallergens. Such allergens can provoke an attack of asthma in a sensitive person and evidence is emerging that effects can be enhanced in the presence of urban pollutants. In the summer months pollen counts may be high during air pollution episodes and it is not clear from epidemiological studies whether there are independent or combined effects of allergens and air pollutants.

2.7 The earlier reports in the present series have provided information to link with air quality "bands" of the type defined by the Department of the Environment for public information purposes, based on concentrations of individual pollutants, ozone, sulphur dioxide and nitrogen dioxide. They have also proposed levels at which warnings would be issued to advise sensitive people about any precautions they might take to avoid adverse reactions. So far this has not taken into account the simultaneous presence of a range of pollutants that is the reality in most current episodes. The following chapters review available knowledge on effects of mixtures with a view to filling the gap and advising on any ways in which overall air quality might be assessed in relation to effects on health.

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Chapter 3

Exposure to Pollutant Mixtures during UK Air Pollution Episodes

Introduction

3.1 Previous reports in this series have discussed the sources, sinks, monitoring techniques and ambient concentrations separately for ozone,[1] sulphur dioxide, acid aerosols and particulates[2] and oxides of nitrogen.[3] This report seeks to examine interactions between these pollutants, and to assess possible health effects resulting from exposure to air pollutant mixtures in the ambient atmosphere.

3.2 The approach adopted in this chapter is as follows: firstly, the United Kingdom's (UK) current air quality monitoring networks are reviewed, with particular emphasis on urban monitoring systems involving sites with co-located measurements of several pollutants. Subsequent analyses then seek to identify what combinations of pollutants may realistically be expected to occur in the UK.

3.3 The correlations between measured concentrations of different pollutants are used to define and describe the generic types of air pollution episodes recorded by the UK monitoring networks. A number of examples of each will be discussed.

3.4 Finally, the frequency of combined pollutant episodes occurring in the UK is assessed and the time of day and the season when these are most likely to occur are identified.

3.5 Clearly it would be desirable to be able to define such episodes in terms that were generally applicable and which would relate the ambient concentrations of pollutants to levels of some standard or guideline. Unfortunately, this is impracticable. The approach used has been to define an indicator pollutant for each type of episode and identify occasions on which exceedence of a specified concentration of that pollutant occurs in combination with elevated levels of other pollutants characteristic of that episode type.

UK air quality monitoring networks

3.6 To provide a comprehensive assessment of UK air quality, the Department of the Environment (DoE) national monitoring networks currently measure pollutant concentrations at 49 automatic monitoring stations and over 1500 sampler sites (involving filter collection of particles, bubbler sampling or passive sampling with diffusion tubes).

3.7 The primary objectives of UK air monitoring systems are to:

- assess population/ecosystem exposure and resulting effects;
- meet present and future statutory requirements under European Community (EC) Directives;
- provide a sound scientific basis for policy development;
- identify long-term trends and major pollutant sources;
- provide information on air quality to the public at large.

In addition, the monitoring results underpin studies to improve our understanding of atmospheric chemistry and the assessment of pollutant emissions.

3.8 Monitoring in the UK is currently organised into 3 automatic networks and 6 sampler-based programmes, details of which are summarised in Table 3.1. The current (1995) automatic network sites are mapped in Figure 3.1.

Site No.	Site Name	Pollutants (see key)	Site No.	Site Name	Pollutants (see key)
1	Straith Vaich	●● ●	26	Bottesford	●
2	Edinburgh Centre	●●●●●	27	Leicester Centre	●●●●●
3	Edinburgh Med S	●	28	Walsall	●
4	Glasgow	●●	29	Aston Hill	●
5	Bush	●	30	Birmingham East	●●●●●●
6	Eskdalemuir	●	31	Birmingham Centre	●●●●●
7	Belfast South	●	32	Sibton	●
8	Newcastle Centre	●●●●●	33	Harwell	●
9	Sunderland	●	34	London UCL	●
10	Great Dun Fell	●	35	London Bloomsbury	●●●●●
11	Belfast Centre	●●●●●	36	Bridge Place	●●●●
12	Belfast East	●	37	Cromwell Road	●●●
13	Wharleycroft	●	38	West London	●●
14	Billingham	●	39	Cardiff East	●
15	Lough Navar	●	40	Cardiff Centre	●●●●●
16	Middlesbrough	●	41	London Bexley	●●●●●
17	High Muffles	●	42	London Eltham	●
18	Leeds Centre	●●●●●	43	Bristol Centre	●●●●●
19	Hull Centre	●●●●●	44	Southampton Centre	●●●●●
20	Barnsley	●	45	Lullington Heath	●●●
21	Manchester	●●	46	Yarner Wood	●
22	Glazebury	●	47	Swansea	●●●●●
23	Liverpool Centre	●●●●●	48	Bristol East	●
24	Sheffield	●●	49	Leeds	●
25	Ladybower	●● ●			

Key ● O_3 ● NO_x ● CO ● SO_2 ● PM_{10} ● HC

Figure 3.1
Department of the Environment automatic air quality monitoring stations in the United Kingdom 1995

Table 3.1
Monitoring networks in the UK, 1995: measurement techniques and objectives

Network:	Urban	Hydrocarbons	Rural	Diffusion tube	Smoke/SO_2	Pb and Multi-elements	Acid deposition	Rural SO_2	Toxic organic micropollutants
Pollutants	O_3, NO_X, SO_2, CO, PM_{10}	27 species	O_3, NO_X, SO_2	NO_2	Smoke/SO_2	Pb, other metals	Anions and Cations	SO_2	PAHs PCBs Dioxins *
Numbers of sites	27 **	9 ***	15 †	1200	225	25	32	29	4
Measurement technique ††	A	A	A	PS	AS	AS	AS,PS	AS	AS
Function †††	S	N	S	N	S	S	N	N	N

* PAH: Polycyclic aromatic hydrocarbon; PCB: Polychlorinated biphenyl; Dioxins: Polychlorinated dibenzo-*p*-dioxins and dibenzofurans

** Includes three affiliated sites, not all sites measure all pollutants

*** Hydrocarbon monitoring at Birmingham East and Middlesbrough is co-located with Urban Affiliate sites

† Includes one site operated by PowerGen, not all sites measure all pollutants

†† A = Automatic, AS = Active Sampler, PS = Passive Sampler

††† S = Statutory, N = Non-Statutory

3.9 Overall objectives are clearly defined for each UK air monitoring network, in order to maximise cost-effectiveness and data utility. Such clearly defined objectives have been set in order to optimise network design, to select priority pollutants and appropriate measurement methods, and to determine the required level of quality assurance/control and data management. In practice, each network meets a different balance of objectives, and is therefore structured, organised and quality-controlled accordingly. The earlier networks were established to fulfil research, policy and statutory functions, whilst the recent urban monitoring initiative has had a primary aim of allowing information on levels of air pollutants to be gathered and distributed to the public.

3.10 This report is concerned with the effects on public health of episodes of air pollution involving elevated concentrations of pollutant mixtures. For many such episodes data from the UK urban networks, and in particular from those using automatic real-time analysers, are of most direct relevance.

3.11 The measurement techniques utilised in current UK automatic air quality monitoring stations are summarised in Table 3.2, together with the numbers of urban measurement locations for each pollutant.

Table 3.2
Urban pollutants: measurement techniques and site numbers

Pollutant	Measurement technique	Numbers of urban sites
Ozone (O_3)	UV absorption	17
Nitrogen oxides (NO, NO_2)	Chemiluminescence	24
Carbon monoxide (CO)	IR absorption	22
Sulphur dioxide (SO_2)	UV fluorescence	21
PM_{10} particulate matter	TEOM *	16
Speciated hydrocarbons	Gas chromatography	9

* Tapered Element Oscillating Microbalance

3.12 Details of current urban air monitoring stations are provided in Table 3.3. Details of the current rural network are provided in Table 3.4. At each station instruments operate which sample and analyse the ambient air automatically. Measurements are stored as 15 minute averages on a data logger which is interrogated automatically via a telephone line to retrieve the results. In the case of automated measurements of hydrocarbons, however, the measurements are made hourly. After data acquisition, the results are processed

centrally by computer and released as provisional statistics, updated hourly, through the DoE's Air Quality Bulletin System. This service feeds information on a variety of pollutants to the public via television and radio weather forecasts, the television services TELETEXT and CEEFAX, newspapers, and a freephone Air Quality Information Service.

Table 3.3
DoE automatic monitoring sites in urban areas — May 1995

County name	Site name	Region name — for press & media	Site type	Pollutants	Start date
Avon	Bristol Centre	Bristol Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/01/93
	Bristol East	Bristol East	Urban Background	VOCs	01/04/94
Belfast	Belfast East	Belfast East	Urban Background	SO_2	06/09/89
	Belfast Centre	Belfast Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	08/03/92
	Belfast Queens Univ.	Belfast South	Urban Background	VOCs	01/03/93
Cleveland	Billingham	Billingham	Urban Industrial	NO_X	01/01/87
	Middlesbrough	Middlesbrough	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	01/04/95
				VOCs	01/01/92
Greater London	Bridge Place	London Victoria	Urban Background	O_3, NO_X, CO, SO_2	01/07/72
	Bexley	London Bexley	Suburban	O_3, NO_X, CO, SO_2, PM_{10}	01/05/94
	Cromwell Road	London Roadside	Roadside	NO_X, CO, SO_2	22/02/73
	West London	London Earls Court	Urban Background	NO_X, CO	01/01/87
	London Bloomsbury	London Bloomsbury	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	23/01/92
	London UCL	London Bloomsbury	Roadside	VOCs	01/12/92
	London Eltham	London Eltham	Suburban	VOCs	01/03/93
Greater Manchester	Manchester	Manchester	Urban Background	NO_X, CO	22/01/87
Hampshire	Southampton Centre	Southampton Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/01/94
Humberside	Hull Centre	Hull Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/01/94
Leicestershire	Leicester Centre	Leicester Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/01/94
Lothian	Edinburgh Centre	Edinburgh Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/10/92
	Edinburgh Med.Sch.	Edinburgh Centre	Urban Background	VOCs	01/06/93
Merseyside	Liverpool Centre	Liverpool Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	23/03/93
South Glamorgan	Cardiff Centre	Cardiff Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	12/05/92
	Cardiff East	Cardiff East	Urban Background	VOCs	01/11/93
South Yorkshire	Sheffield	Sheffield	Urban Industrial	NO_X, CO	28/11/90
	Barnsley 12	Barnsley	Urban Background	SO_2	14/03/91
Strathclyde	Glasgow	Glasgow	Urban Background	NO_X, CO	06/01/87
Tyne & Wear	Sunderland	Sunderland	Urban Background	SO_2	06/10/92
	Newcastle Centre	Newcastle Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	08/03/92
West Glamorgan	Swansea Centre	Swansea Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	01/12/94
West Midlands	Walsall	Walsall	Urban Industrial	NO_X	05/03/87
	Birmingham Centre	Birmingham Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	18/03/92
	Birmingham East	Birmingham East	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	01/12/93
				VOCs	01/08/93
West Yorkshire	Leeds	Leeds Centre	Urban Background	O_3, NO_X, CO, SO_2, PM_{10}	04/01/93
	Leeds Potternewton	Leeds Centre	Urban Background	VOCs	23/12/94

3.13 The UK air monitoring networks have evolved substantially over recent years, and this expansion of both pollutant coverage and site numbers is likely to continue to increase in the future. However, it should be recognised that the historic dataset of co-located multi-pollutant measurements, which is fundamental to assessing the health impacts of combinations of pollutants, is relatively limited.

3.14 The automatic urban network, measuring a range of pollutants at urban locations throughout the country, is an important source of data. This network was established in 1992, and therefore three years or less of data are available. Moreover, both 1992 and 1993 proved to be 'quiet' in pollution terms, with relatively limited numbers of episodes when levels of pollutants were high.

3.15 Conversely, whilst over twenty years of measurements are available for some urban monitoring stations such as Central London, there are relatively few such sites and the range of pollutants measured is smaller. Data from all urban sites will be utilised in this report.

3.16 Further planned expansion of urban monitoring, together with the incorporation of selected quality-controlled Local Authority stations, will result in both substantially increased site numbers and greater availability of combined multi-pollutant measurements in urban areas.

Table 3.4
DoE automatic monitoring sites in rural areas — May 1995

County name	Site name	Region name — for press and media	Site type	Pollutants	Start date
Cheshire	Glazebury	Cheshire	Suburban	O_3	01/04/88
Cumbria	Great Dunn Fell	Mountain peak	Mountain top	O_3	09/05/86
	Wharleycroft	Cumbria	Rural	O_3	08/05/85
Derbyshire	Ladybower	Derbyshire	Rural	O_3, NO_X, SO_2	15/07/88
Devon	Yarner Wood	Devon	Rural	O_3	26/06/87
Dumfries & Galloway	Eskdalemuir	South Scotland	Rural	O_3	23/04/86
East Sussex	Lullington Heath	East Sussex	Rural	O_3, NO_X, SO_2	04/10/86
Fermanagh	Lough Navar	Northern Ireland	Remote	O_3	02/04/87
Highland	Strath Vaich	North Scotland	Remote	O_3, NO_X, SO_2	18/03/87
Lothian	Bush	South Scotland	Rural	O_3	01/04/86
North Yorkshire	High Muffles	North Yorkshire	Rural	O_3	16/07/87
Nottinghamshire	Bottesford	Nottinghamshire	Suburban	O_3	01/10/77
Oxfordshire	Harwell	Oxfordshire	Rural	O_3	22/06/76
Powys	Aston Hill	Mid-Wales	Rural	O_3	26/06/86
Suffolk	Sibton	East Anglia	Rural	O_3	01/07/73

Correlations between measured pollutant concentrations

3.17 In this section the correlations between measured hourly average pollutant concentrations are examined both over the entire urban network and at individual sites. Correlation coefficients between pairs of pollutants have been calculated for the two year period from establishment of the network in January 1992 until December 1993

3.18 Inter-correlations of pollutants within the urban network are presented as a simple colour-coded matrix in Figure 3.2a. One of its most obvious features is the lack of any significant positive correlation between measured concentrations of ozone (O_3) and those of other pollutants. There are, however, reasonably strong negative correlations of O_3 with both nitrogen dioxide (NO_2) and total oxides of nitrogen (NO_X), reflecting the chemical equilibrium between these species in the atmosphere. As will be shown, elevated concentrations of other pollutants can occur during ozone episodes; however, the photochemical reactions which are the main feature of such episodes cause the times at which peak pollutant concentrations occur to be separated.[1,4]

3.19 From a limited set of co-located and concurrent measurements throughout the urban network as a whole, Table 3.5 demonstrates that concentrations of most pollutants are depressed during those hours when hourly average concentrations of O_3 exceed 90 ppb (180 $\mu g/m^3$). The only exception to this is for particulate matter, measured as PM_{10}, for which concentrations during such periods tend to exceed typical long-term baseline levels of 20-30 $\mu g/m^3$. The reason for this is the production of photochemically-generated aerosol particles, visible as the familiar haze on some hot, sunny days. Regression analyses over the whole year (as in Figure 3.2) can conceal correlations occurring during particular seasons; analysis of data from a single, central London, site over the summer months of 1993 and 1994 reveals a significant correlation of O_3 and PM_{10} levels measured on the same day (Figure 3.3). However, similar analyses of data from other urban sites has shown year-to-year variability with a lack of correlation in some summers (data not shown). If the correlation of Figure 3.3 persists in analyses of data from additional sites in future years then the relationship will be important in two respects.

Firstly, there is the potential for additive, or possibly synergistic, effects on health from O_3 and PM_{10} during photochemical episodes. Secondly, from a control and abatement policy point of view, the particle concentrations in such periods may be significantly influenced by long range, transboundary, transport of sulphate and nitrate aerosols.

Table 3.5

Urban network pollutant concentrations (means of hourly averages) during periods with hourly O_3 concentrations ≥ 90 ppb, 1/1/92 to 31/12/93

Pollutant	Concentration * (ppb, unless otherwise indicated)	Ratio to period mean **	Number of measurements
O_3	94	6.7	13
NO_2	13	0.5	13
NO_X	14	0.2	13
CO	0.5 (ppm)	0.7	13
PM_{10}	40 ($\mu g/m^3$)	1.6	13
SO_2	5	0.5	13

* These values are based on available concurrent and co-located measurements

** This ratio is obtained by dividing the mean hourly average concentration of the pollutant (in the previous column by the mean hourly average concentration over the whole period from 1/1/92 to 31/12/93

Figure 3.2 **Correlations between hourly average pollutant concentrations in the urban network for 1992-1993.** a) **Across the whole network in 1992 and 1993, based on 75,982 - 100,231 co-located values;** b) **London, Bloomsbury site for 1992 and 1993, based on 13,601 - 16,422 values;** c) **London, Bloomsbury site at periods when the NO_2 concentration was > 100 ppb, based on 11 - 15 values;** d) **Belfast centre site for 1992 and 1993, based on 13,505 - 15,448 values.**

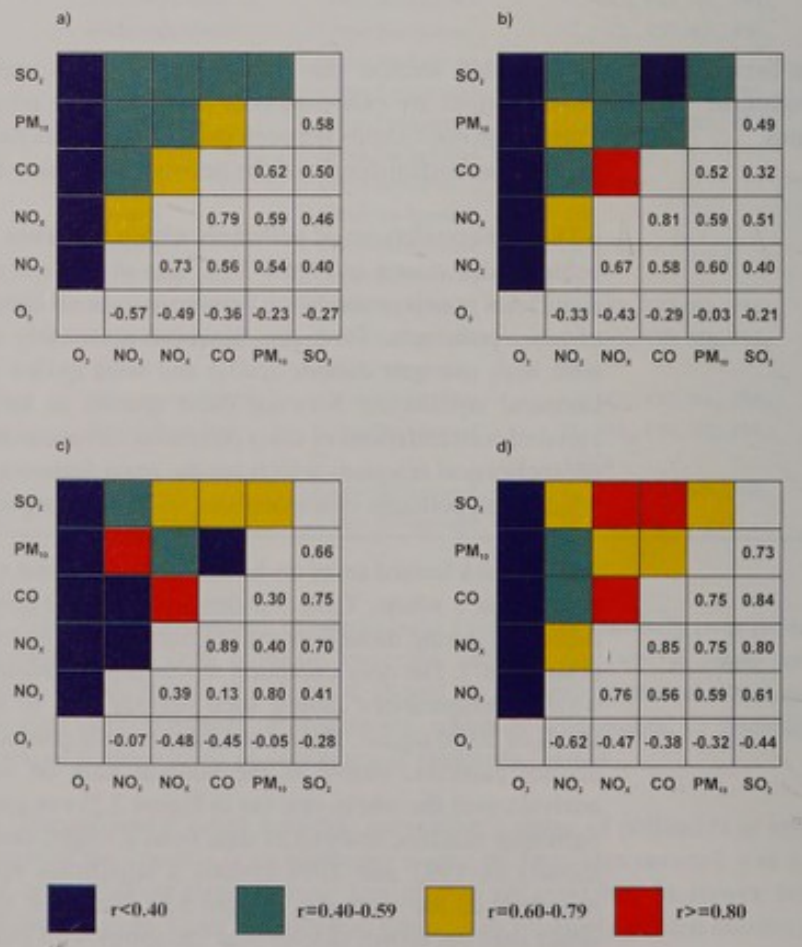
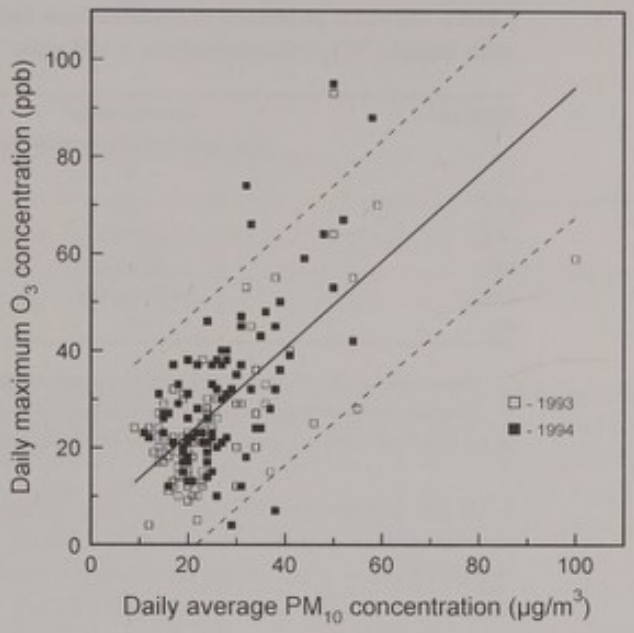


Figure 3.3 **Correlation, during the months of June to August in the years 1993 and 1994, of the daily mean concentration of PM_{10} ($\mu g/m^3$) with the daily maximum hourly concentration of O_3 (ppb) at London, Bloomsbury site. Individual values are plotted with the regression line with 95% confidence limits. Equation of the line is $[O_3] = 0.897[PM_{10}] + 4.66$, correlation coefficient (r) = 0.658.**



3.20 It is interesting to note that data from a long-running rural monitoring site with co-located O_3 and aerosol measurements indicates some correlation between O_3 and total aerosol acidity (H^+), but not with total sulphate ion (SO_4^{2-}) or nitrate ion (NO_3^-, data not shown). This relationship appears, however, to be seasonally dependent (see Table 3.6).

3.21 It is readily apparent that the strongest observed pollutant 'cluster' in Figure 3.2a is that between carbon monoxide (CO), nitrogen dioxide (NO_2), oxides of nitrogen (NO_X) and particulate matter (PM_{10}). This is clearly due to motor vehicle emissions, which are the most important source of these pollutants in UK urban environments.

Table 3.6
Correlations between sulphate ion, acid aerosol*, and ozone at Harwell (1983-1991)

Pollutant measures	Time of year	Correlation coefficient (r)	Significance (p)
SO_4^{2-} *vs* maximum hourly O_3 of day	All months	0.068	0.524
	March - June	0.073	0.681
	September - December	–0.144	0.484
SO_4^{2-} *vs* mean hourly O_3 of day	All months	–0.002	0.987
	March - June	–0.030	0.868
	September - December	–0.142	0.488
H^+ *vs* maximum hourly O_3 of day	All months	0.378	0.011
	March - June	0.486	0.078
	September - December	0.017	0.953
H^+ *vs* mean hourly O_3 of day	All months	0.194	0.208
	March - June	–0.053	0.856
	September - December	–0.615	0.019

* Calculated value derived from ion balance

3.22 The vehicle emissions cluster may be further investigated within the urban background sites as a whole by calculating mean co-located pollutant concentrations during episodes with hourly NO_2 concentrations exceeding 100 ppb (188 $\mu g/m^3$), see Table 3.7. The 100 ppb figure used here corresponds to the lower limit of the DoE **'Poor'** air quality band and is similar to the EC Directive 98th percentile, of hourly means, limit value (104.6 ppb, 200 $\mu g/m^3$) for this pollutant. Whilst Figure 3.2a, not surprisingly, shows elevated concentrations of CO and PM_{10} during such periods, sulphur dioxide (SO_2) levels also appear to be elevated. During 63 such episodes recorded by the urban

network during 1992 and 1993, it is interesting to note that overall average concentrations of individual pollutants were 3.2 ppm (4 mg/m^3) for CO, 127 µg/m^3 for PM_{10} and 57 ppb (163 µg/m^3) for SO_2.

Table 3.7

Urban network pollutant concentrations (means of hourly averages) during periods with hourly NO_2 concentrations ≥ 100 ppb, 1/1/92 to 31/12/93

Pollutant	Concentration* (ppb, unless otherwise indicated)	Ratio to period mean **	Number of measurements
O_3	9	0.6	52
NO_2	126	4.7	63
NO_X	530	8.3	61
CO	3.2 (ppm)	4.6	59
PM_{10}	127 (µg/m^3)	4.6	49
SO_2	57	5.7	59

* These values are based on available concurrent and co-located measurements

** This ratio is obtained by dividing the mean hourly average concentration of the pollutant (in the previous column) by the mean hourly average concentration over the whole period from 1/1/92 to 31/12/93

3.23 The urban network has sites in a variety of cities throughout the UK. Belfast, in particular, has a different pollutant climate from most other UK cities, due to the extensive use of coal and oil for domestic heating. Using London as an archetype for UK cities shows a more typical pollutant mixture during NO_2 episodes (Table 3.8).

Table 3.8

Pollutant concentrations at London Bloomsbury (means of hourly averages) during periods with hourly NO_2 concentrations ≥ 100 ppb, 23/1/92 to 31/12/93

Pollutant	Concentration (ppb, unless otherwise indicated)	Ratio to period mean*	Number of measurements
O_3	6	0.7	13
NO_2	109	3.2	14
NO_X	395	5.3	14
CO	3.1 (ppm)	4.4	13
PM_{10}	109 (µg/m^3)	3.8	11
SO_2	39	3.4	13

* This ratio is obtained by dividing the mean hourly average concentration of the pollutant (in the previous column) by the mean hourly average concentration over the whole period from 23/1/92 to 31/12/9

3.24 The $NO_2/NO_X/CO/PM_{10}$ cluster of vehicle-derived pollutants is shown even more clearly when examining data from the London Bloomsbury site in isolation, see Figures 3.2b and 3.2c. A particularly strong CO/NO_X relationship is evident in both figures. It is also interesting to note a strong NO_2/PM_{10} correlation during NO_2 episodes (Figure 3.2c). Since NO_2 is mainly a secondary pollutant, much of which is formed chemically in the atmosphere from primary NO emissions,[3.5] this observation may suggest a similar secondary contribution of nitrate aerosols to PM10 levels during such periods, but this is speculative at present.

3.25 The mean concentrations of individual pollutants associated with SO_2 episodes in UK cities are listed in Table 3.9. Utilising data from the entire urban network, an SO_2 episode is defined as a period with an hourly average concentration exceeding 125 ppb (357 µg/m^3). This level corresponds to the lower limit of the DoE **'Poor'** air quality band and is similar to the current World Health Organization (WHO) 1-hour guideline for this pollutant (122 ppb, 350 µg/m^3).

Table 3.9

Urban network pollutant concentrations (means of hourly averages) during periods with hourly SO_2 concentrations ≥ 125 ppb, 1/1/92 to 31/12/93

Pollutant	Concentration* (ppb, unless otherwise indicated)	Ratio to period mean **	Number of measurements
O_3	7	0.5	152
NO_2	58	2.2	148
NO_X	367	6.0	148
CO	6.0 (ppm)	8.6	155
PM_{10}	207 ($\mu g/m^3$)	7.5	145
SO_2	172	17.1	155

* These values are based on available concurrent and co-located measurements

** This ratio is obtained by dividing the mean hourly average concentration of the pollutant (in the previous column) by the mean hourly average concentration over the whole period from 1/1/92 to 31/12/9

3.26 It should be recognised that most of the 155 such episodes observed in the urban network during 1992/93 occurred at the Belfast Centre site. Table 3.10 shows measured concentrations during such Belfast SO_2 episodes. Elevated mean concentrations of NO_2 (61 ppb, 115 $\mu g/m^3$), NO_X (415 ppb), CO (7.5 ppm, 9.4 mg/m^3) and PM_{10} (248 $\mu g/m^3$) were recorded during these episodes. The corresponding correlation matrix (Figure 3.2d) shows the strong positive correlations between all pollutants except ozone at Belfast. The particularly strong negative correlation between measured O_3 and NO_2 concentrations at this location should be noted. Belfast can usefully be described as a location characterised by mixed sources of pollutants: motor vehicles and solid fuel.

Table 3.10

Pollutant concentrations at Belfast Centre (means of hourly averages) during periods with hourly SO_2 concentrations ≥ 125 ppb, 8/3/92 to 31/12/93

Pollutant	Concentration (ppb, unless otherwise indicated)	Ratio to period mean*	Number of measurements
O_3	8	0.5	114
NO_2	61	2.8	115
NO_X	415	8.9	115
CO	7.5 (ppm)	10.7	115
PM_{10}	248 ($\mu g/m^3$)	8.3	109
SO_2	179	10.7	115

* This ratio is obtained by dividing the mean hourly average concentration of the pollutant (in the previous column) by the mean hourly average concentration over the whole period from 8/3/92 to 31/12/93

Case studies of combined air pollutant episodes

3.27 In the previous section, correlations between measured concentrations of pollutants in UK cities were examined in an attempt to identify characteristic clusters of pollutants occurring during periods of elevated concentrations. Analyses demonstrated a lack of positive correlation between ozone and most other pollutants, a clear $NO_2/NO_X/CO/PM_{10}$ vehicle cluster, and a strong relationship between all pollutants except ozone at locations with mixed pollutant sources.

3.28 A number of combined air pollutant episodes are now examined. Not surprisingly, these appear to fall into three main generic types:

- Type 1 Summer Smog O_3, PM_{10}, (NO_2)
- Type 2 Vehicle Smog NO_2, PM_{10}, CO
- Type 3 Winter Smog (mixed sources) SO_2, PM_{10}, CO, (NO_2)

3.29 In these episode archetypes, bracketed pollutants identify species that appear to be

of less importance in the mixture, either being less strongly correlated with other pollutants or being present at lower ambient concentrations.

3.30 Air pollution episodes occur in the UK when there is an appropriate combination of emissions of pollutants, meteorological conditions and atmospheric chemical reactions. The influence of these different factors will be described in the case studies below.

3.31 Pollutant episodes in the summer (Type 1) are associated with anticyclonic conditions, light winds, high temperatures and sunshine. Primary emissions of volatile organic compounds and oxides of nitrogen undergo chemical reactions in the atmosphere to produce elevated concentrations of oxidants such as O_3, NO_2 and peroxyacetyl nitrate (PAN). The atmospheric chemistry of such episodes is fully reviewed in the Ozone report of this series,[1] and elsewhere.[4]

3.32 Summer Type 1 episodes tend to affect large areas of the country, both urban and rural. Airmass history is an important feature of summer episodes, which may often be associated with the transport of polluted air over considerable distances from the site of production of the original precursor emissions.[4] As will be shown, the characteristic chemistry of such episodes results in concentrations of precursor species such as NO_X being temporally and spatially decoupled from those of oxidant end-products such as O_3 or NO_2. By their nature, therefore, these are not combined episodes with simultaneous peaks of different pollutants.

3.33 Levels of photolytically-generated atmospheric oxidants such as O_3, the hydroxy radical ($HO\cdot$) and the hydroperoxy radical ($HO_2\cdot$) are generally much lower during winter air pollutant episodes, and atmospheric chemistry therefore plays a less important rôle in Type 2 winter or Type 3 episodes. These are associated with anticyclonic conditions, light winds or calms, low temperatures and shallow mixing layer depths. Stable meteorological conditions, often associated with fog, tend to be the characteristic trigger for such winter episodes. For the most part, chemical reactions in the atmosphere tend to be slower and less influential in determining the final episode pollutant mix. Heterogeneous chemistry may also become more important.

3.34 Type 2 and 3 episodes are associated with simultaneously elevated concentrations of a range of pollutants; the resulting mixture depends on the main pollutant emission sources. In most UK cities, motor vehicle emissions represent the major source of pollution, leading to Type 2 episodes. In cities such as Belfast where domestic space heating contributes significantly to the atmospheric pollutant burden, the more diverse emission profile results in Type 3 episodes.

3.35 Over the last 40 years there has been a change in the type of air pollution episode experienced in the UK. Winter SO_2/Suspended Particulate Matter (SPM) episodes caused by coal burning in cities have ceased and been replaced by, firstly, mixed domestic/vehicle episodes (Type 3), which still occur in Belfast, and, more recently, by vehicle-related episodes (Type 2) which can now occur in most cities.

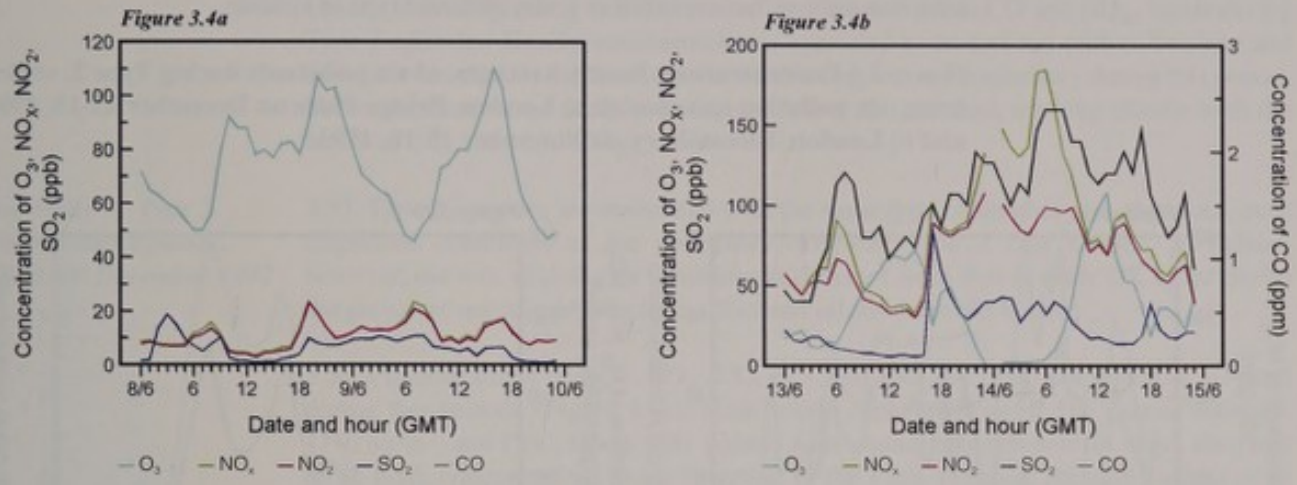
3.36 To clarify and demonstrate the main features of UK episode types, a number of episodes which have occurred during the last six years are now reviewed.

3.37 As indicated previously, summer photochemical episodes can occur in rural or urban areas. Peak ozone concentrations are usually higher in rural areas, while concentrations of most other pollutants generally remain low.

Case Study 1: Type 1 Rural Episode, Lullington Heath, 8-9 June 1993

3.38 This particular rural episode (Figure 3.4a) was characterised by high pressure over northwest Europe. Ozone concentrations were elevated over much of the UK, and in particular on June 9th. Slow-moving airmasses brought ozone precursors of European origin to this location in southeast England. This air was well aged, as demonstrated by the very low nitric oxide (NO) concentrations (shown by the concentrations of NO_2 and NO_X being similar). Corresponding NO_2 and SO_2 concentrations were also low. It should be noted that there is no co-located measurement of acid aerosols or PM_{10} at Lullington Heath.

Figure 3.4 **Concentrations, hourly averages, of air pollutants during Type 1, summer, air pollution episodes at: a) a rural site, Lullington Heath on June 8-9, 1993, and b) an urban site, London, Bridge Place on June 13-14, 1989.**



3.39 This is a typical 'ozone only' Type 1 episode in a rural area. Although, on occasions, less well aged UK-sourced precursors contribute to summer episodes, concentrations of other species usually remain low during such periods.

Case Study 2: Type 1 Urban Episode, London, 13-14 June 1989

3.40 Summer smog episodes in urban areas are characterised by high ozone concentrations and, frequently, elevated NO_2 levels. However, peak concentrations of these pollutants do not occur at the same time. The oxidant present as O_3 in rural areas during summer episodes can be expressed in cities as either O_3 or NO_2. The resulting pollutant mixture during any episode will depend both on meteorological conditions and the magnitude of local NO_X emissions.

3.41 In this case study (Figure 3.4b), elevated concentrations of both NO_2 and O_3 were recorded. As in the previous case study, this episode was associated with the long-range transport of ozone, over distances of hundreds of kilometers, from source areas in Europe. However, to this mix was added NO_X emissions from motor vehicles in the London area itself. The resulting episode, as it developed over time, demonstrated a complex balance between ozone transport from outside London, local emission patterns, meteorology and vertical dispersion.

3.42 During the episode there was a clear negative correlation between O_3 and NO (NO data not shown). This is hardly surprising, as the two react together rapidly to produce NO_2. In the early hours of the 14th, all available O_3 in the shallow nocturnal boundary layer had been depleted to generate over 100 ppb (188 $\mu g/m^3$) of NO_2. Concentrations of NO rose rapidly during the rush hour period, only to be consumed with the onset of convective mixing, which allowed reaction with the higher altitude reservoir of long-range transported O_3 above the night-time boundary layer.

3.43 Whilst the peaks of O_3 and NO_2 rarely coincide, this case study demonstrates that elevated concentrations of both pollutants can be experienced at the same place over a period of a few hours.

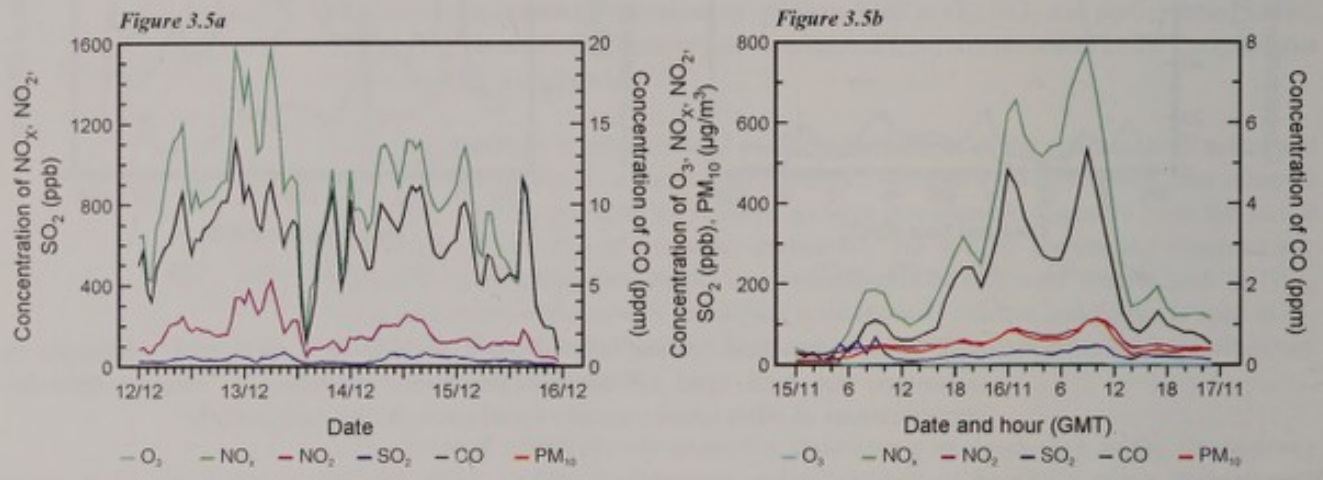
Case Study 3: Type 2 Urban Vehicle Episode, London, 12-15 December 1991

3.44 The characteristics and atmospheric chemistry of this well-publicised and documented episode have been thoroughly reviewed elsewhere[6] Although more than usually severe, it may be regarded as the archetypal modern UK urban winter episode. Concentrations of NO_2 at background monitoring sites in London during the second week of December were the highest recorded in the UK since uninterrupted automatic monitoring began in the early 1970s.

3.45 In contrast to summer smog episodes, which are characterised by photochemical oxidant chemistry and long-range transport, winter episodes result from stagnation

conditions in shallow mixing layers. Meteorological conditions during the December 1991 episode were cold, stable and anticyclonic, with frequent freezing fogs. These conditions were very similar to weather patterns associated with the severe London smoke/SO_2 smogs during the 1950s and 1960s. However, in the 1990s, changing emission patterns have resulted in a very different type of episode.

Figure 3.5 **Concentrations, hourly averages, of air pollutants during Type 2, vehicle smog, air pollution episodes at: a) London, Bridge Place on December 12-15, 1991, and b) London, Bloomsbury on November 15-16, 1993.**



3.46 Concentrations of CO were also elevated (maximum hourly average of about 15 ppm, 19 mg/m^3) during the episode (Figure 3.5a), and these were strongly correlated with both NO_2 and NO_X concentrations. The observed CO/NO_X ratios seen here are broadly consistent, as expected, with the corresponding vehicle emission rates.

3.47 Levels of SO_2 during the episode were, however, low and did not correlate with those of CO or NO_X. Corresponding O_3 concentrations, not shown, were strongly depressed, being depleted by reaction with primary NO_X emissions.

3.48 A variety of analyses have demonstrated traffic emissions as the dominant source of pollution during the episode.[6] Further analysis and modelling of the episode period shows that the extreme NO_2 concentrations are explainable, at least in part, by enhanced gas-phase oxidation of NO to NO_2 at low temperatures and high NO concentrations:

$$2\,NO + O_2 \rightarrow 2\,NO_2$$

This reaction is slower than the fast oxidation by ozone which can occur during Type 1 summer episodes:

$$NO + O_3 \rightarrow NO_2 + O_2$$

3.49 Although vehicle-related pollutants were elevated in other parts of the country during this period, levels were not as extreme as in London. Unlike Type 1 summer episodes, which can occur over large parts of the country (or even on a regional scale), local topography, frost pockets, broken cloud cover and local emission densities can exert a strong influence on the development of Type 2 winter episodes.

Case Study 4: Type 2 Urban Vehicle Episode, London, 15-16 November 1993

3.50 This episode was of shorter duration than that of case study 3, and generally lower pollutant concentrations were observed (Figure 3.5b). This is not surprising: the longer such a Type 2 episode continues without pollutants being effectively dispersed, the greater the build-up of pollutants. As a result, there is a strong and direct link between the duration of UK stagnation episodes and the magnitude of peak pollutant concentrations[6].

3.51 It may also be noted, in passing, that there is a strong historic predisposition

towards extended periods of stable, foggy weather – favourable for pollution episodes in London – during the first 2-3 weeks of December.

3.52 The episode is graphed here in order to show that elevated PM_{10} levels, tracking closely to corresponding 'vehicle-cluster' pollutants such as CO and NO_X, occur during Type 2 episodes. Hourly measurements of speciated hydrocarbons such as benzene and toluene were also available at a nearby monitoring site in Bloomsbury during this period. The concentrations of these hydrocarbons were also elevated, tracking closely with the levels of CO, NO_X and PM_{10}.

Case Study 5: Type 3 Urban Winter Episode, Belfast, 20 December 1992

3.53 Type 3 episodes are associated with the same type of weather and, therefore, poor dispersion conditions as the previously reviewed Type 2 case studies. In Belfast, however, the mix of pollutant emissions is different from that in other UK cities due to the prevalent use of coal, smokeless fuel and oil for domestic heating.

3.54 Concentrations of NO_2, NO_X, CO, SO_2 and PM_{10} were all considerably elevated during this episode (Figure 3.6a). Peak hourly concentrations of SO_2 (about 400 ppb, 1140 $\mu g/m^3$) and PM_{10} (about 900 $\mu g/m^3$) were particularly noteworthy. Note, also, that these peak concentrations were observed in the early evening, strongly indicative of space heating emission patterns.

3.55 Another interesting feature of this Type 3 episode is that ozone concentrations peaked at about 15 ppb (30 $\mu g/m^3$) — this contrasts strongly with the corresponding near-zero concentrations observed in Type 2 winter episodes in London. The reasons for this are not at present clear.

Case Study 6: Type 3 Urban Winter Episode, Belfast, 26 November 1993

3.56 This episode differs from case study 5 in its time of occurrence. Concentrations of pollutants peaked before midday, with relatively lower levels of SO_2 and PM_{10} but comparable CO, NO_2 and NO_X levels (Figure 3.6b). This is, of course, consistent with a greater relative contribution from traffic rather than domestic space heating emissions.

3.57 As in case study 5, concentrations of all pollutants track extremely closely during this episode.

Figure 3.6 **Concentrations, hourly averages, of air pollutants during Type 3, winter, air pollution episodes at Belfast Centre on;** a) **December 20, 1992, and** b) **November 26, 1993.**

Figure 3.6a

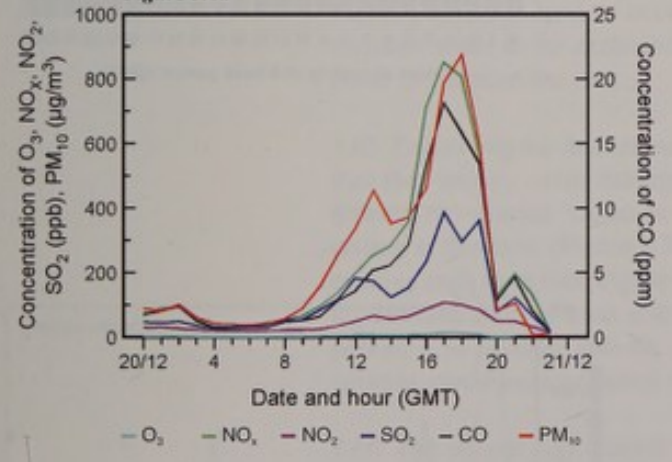
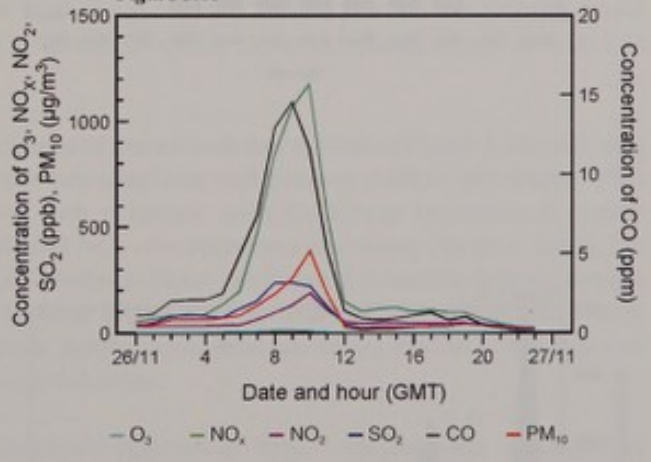


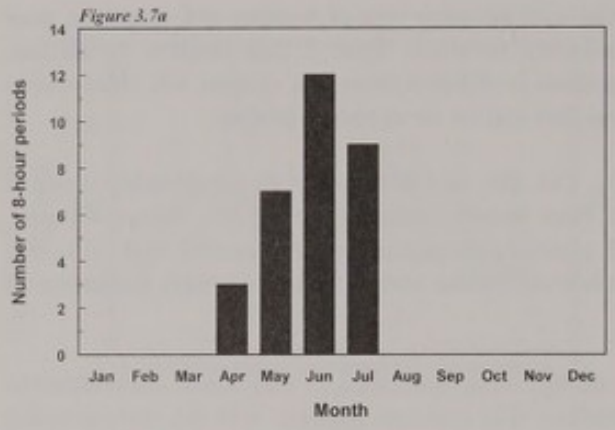
Figure 3.6b

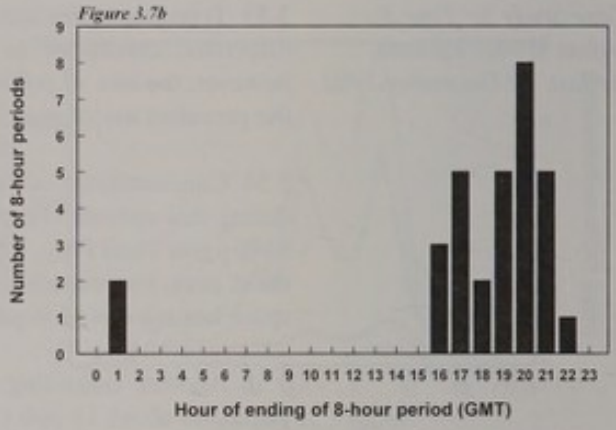


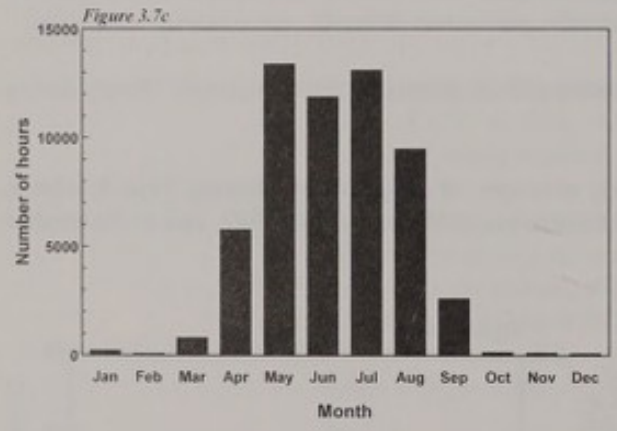
General characteristics of combined air pollutant episodes

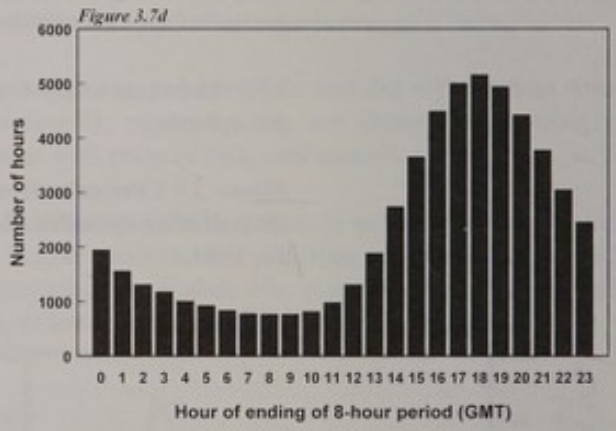
3.58 In this section, the general characteristics of the episode types discussed previously will be reviewed. In addition, the distribution of episode numbers throughout the year (monthly incidence) as well as during the day (diurnal incidence) will be examined. Average episode durations and trends in episode numbers over time will also be investigated.

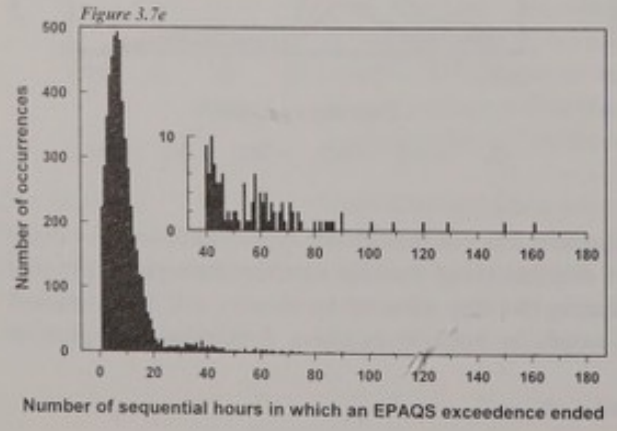
Figure 3.7 **Analysis of Type 1, summer smog, episodes. a) Monthly incidence of occasions when the running average 8-hour O_3 concentration exceeded 50 ppb and a co-located hourly average NO_2 concentration ≥ 50 ppb occurred during this 8-hour period, data from the urban network during 1992-1993; b) Diurnal incidence of the hour at which the combined O_3/NO_2 episodes defined in a) above ended; c) Monthly incidence of occasions when the running average 8-hour O_3 concentration exceeded 50 ppb (an EPAQS ozone exceedence), data from all available sites during 1972-1993; d) Diurnal incidence of the hour at which the ozone episodes defined in c) above ended; e) Duration of episodes in which EPAQS ozone exceedences occurred, data from all available sites during 1972-1993; f) Annual incidence of EPAQS ozone exceedences in Central London during 1972-1993.**

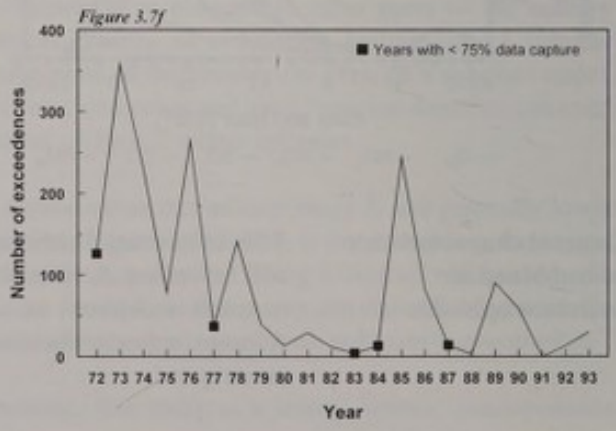












3.59 The limited database for co-located measurements means that to do this in a useful way it is necessary to choose between two general analytical approaches. Firstly, the incidence of mixed pollutant episodes using co-located urban network measurements from 1992-1993 may be examined. This approach, which is based on the data from two fairly unrepresentative years, involves limited episode numbers and may therefore lack statistical robustness. Any conclusions may not necessarily be representative in the long term.

3.60 Alternatively, indicator pollutants may be selected for each episode type, and these can then be analysed in isolation. For the three episode types, the following indicator pollutants have been chosen:

- Type 1 Summer Smog O_3
- Type 2 Vehicle Smog NO_2
- Type 3 Winter Smog (mixed sources) SO_2

3.61 This approach, following some of the analyses in previous reports in this series, has the advantage of being based on considerably more extended datasets with greater episode numbers. It is, however, indirect and attempts to infer the incidence of mixed episodes from analyses of one of the major components of the pollutant mixture.

3.62 Where appropriate, both approaches are used in the following analyses.

Type 1, Summer Smog Episodes

3.63 As has been shown, episodes of this type are not characterised by simultaneously elevated concentrations of a range of pollutants. However, in cities these episodes can result in high O_3 and NO_2 concentrations usually separated by 3-4 hours. The occurrence of such 'fuzzy' combined episodes may be examined by considering occasions when:

(i) The recently recommended Expert Panel on Air Quality Standards (EPAQS) running 8-hour standard of 50 ppb (100 $\mu g/m^3$) for ozone[7] is exceeded, and

(ii) NO_2 levels are also elevated within this 8-hour period. For this purpose, a trigger threshold of an NO_2 hourly average > 50 ppb, 94 $\mu g/m^3$ (the transition between the DoE '**Very Good**' to '**Good**' air quality bands) is used.

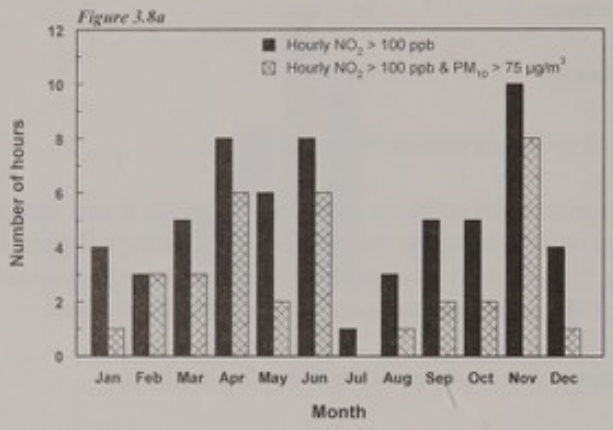
3.64 The annual and diurnal incidence of such Type 1 episodes in the urban network are illustrated in Figures 3.7a and 3.7b. Figure 3.7a shows, not surprisingly, that combined O_3/NO_2 episodes tend to occur from April to July. This is because the EPAQS ozone standard tends to be exceeded in summer,[7] whilst elevated concentrations of NO_2 can occur throughout the year.

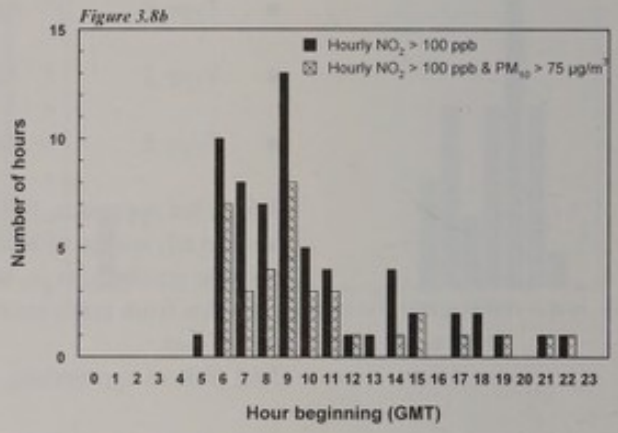
3.65 Examining the diurnal incidence of these combined episodes (Figure 3.7b) indicates that they mostly occur during the late afternoon and evening (1600-2200 hours). This reflects the diurnal variation of each pollutant, with O_3 8-hour exceedences mostly ending at this time (Figure 3.7d) and NO_2 concentrations also being elevated during the evening rush hour (see Figure 3.8d below). However, because a running 8-hour average O_3 concentration is used and because Figure 3.7b records the end of such an 8-hour period, it is possible that the peak hourly concentrations of O_3 and NO_2, for any one episode, could have occurred at earlier times.

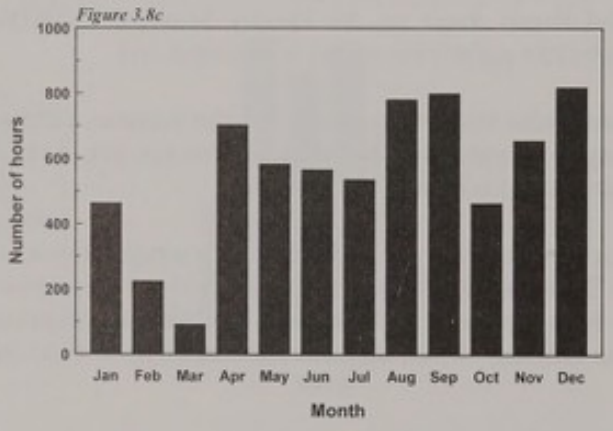
3.66 The annual and diurnal incidence patterns of Type 1 episodes are illustrated in Figures 3.7c and 3.7d respectively. In this case, however, the exceedences of the 8-hour EPAQS standard are examined in isolation, and data from all UK ozone measurement sites operational since 1972 are used. In practice, these analyses will be biased towards the period since 1986, when the number of sites began to increase substantially.

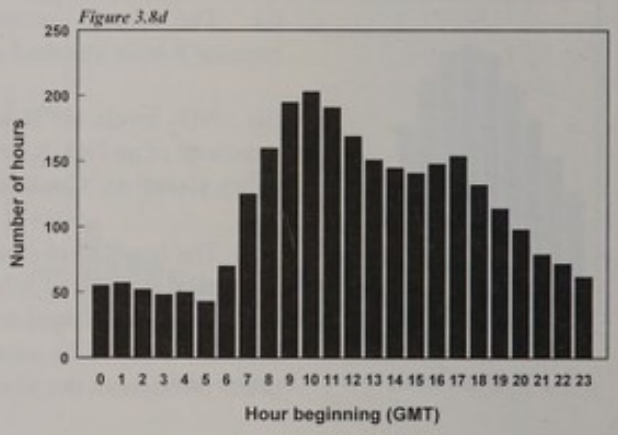
3.67 The expected tendency of ozone episodes to occur in the mid-summer months from

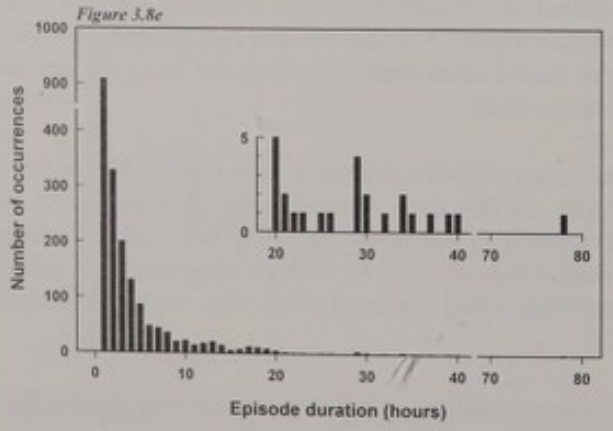
Figure 3.8 **Analysis of Type 2, vehicle smog, episodes. a) Monthly incidence of occasions when the hourly average NO_2 concentration exceeded 100 ppb and when both the hourly NO_2 concentration exceeded 100 ppb and the co-located hourly average concentration of PM_{10} exceeded 75 µg/m^3, data from the urban network during 1992-1993; b) Diurnal incidence of the hours in which NO_2 and combined NO_2/PM_{10} episodes as defined in a) above occurred; c) Monthly incidence of occasions when hourly average concentration of NO_2 exceeded 100 ppb, data from all available sites, 1972-1993; d) Diurnal incidence of the hours in which hourly average NO_2 concentrations exceeded 100 ppb during the winter months of October-March, data from all sites 1976-1993; e) Duration in hours of episodes when NO_2 hourly average concentrations exceeded 100 ppb, data from all sites 1976-1993; f) Annual incidence of episodes with an hourly average concentration of NO_2 exceeding 100 ppb, data from Central London.**

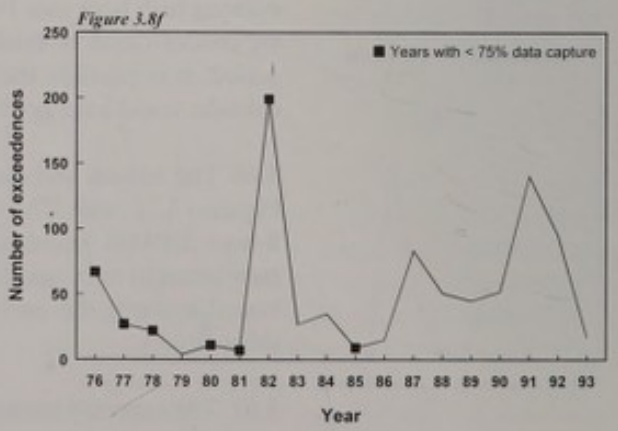












May to August, when sunshine levels and average temperatures are highest, is illustrated in Figure 3.7c. These patterns, of course, may be expected to change from year to year, although episodes earlier than April or later than September would be extremely unusual in any year.

3.68 Ozone episodes with a running 8-hour average greater than 50 ppb (100 $\mu g/m^3$) occur most frequently in the period from about 1300-2300 hours (Figure 3.7d). This is consistent with previous analyses.[1] These have shown that elevated hourly average concentrations occur most frequently after midday, and that the highest levels are usually in mid-afternoon (about 1400 hours) when the boundary layer is well mixed and photochemical activity at its highest.

3.69 It is apparent from Figure 3.7e that once an EPAQS exceedence has been recorded, there will usually continue to be exceedences in subsequent hours. The number of consecutive hours during which exceedences continue is most commonly 6-8 hours, however, very few exceed 20 hours in duration. It should be noted that previous analyses in this series have demonstrated a tendency for O_3 episodes to occur on up to 3-5 consecutive days in sequence.[1,4,8,9]

3.70 Episode numbers at a long-running urban site, Central London, from 1972 to 1993 are shown in Figure 3.7f. Only a very few UK air quality monitoring sites have a sufficiently extended measurement history to facilitate meaningful trend analysis; even at this site, the period of operation has included two necessary minor relocations in 1976 and 1990.

3.71 The year-on-year variation in ozone episode numbers is readily apparent from Figure 3.7f. There is a marked contrast between years with long, hot, sunny summers, such as 1973, 1976, 1978, 1985 and 1989-1990, and quieter periods such as 1980-1983, 1987-1988 and 1991-1993. It is, however, interesting to note that two of the hottest summers on record, in 1989 and 1990, resulted in lower episode numbers than previous, cooler periods.

3.72 A variety of analyses suggest that there is a downward trend in the numbers of ozone episodes occurring at sites in London and southeast England, consistent with increasing NO_X emissions, and therefore increased reaction of O_3 with NO, in these areas.[8] However, data from the rural ozone network, established in 1986, indicate that this trend may not apply throughout the UK.[9] The urban network dataset, starting in 1992, is, as yet, too short to allow trend analysis to define changing episode numbers over time in UK cities.

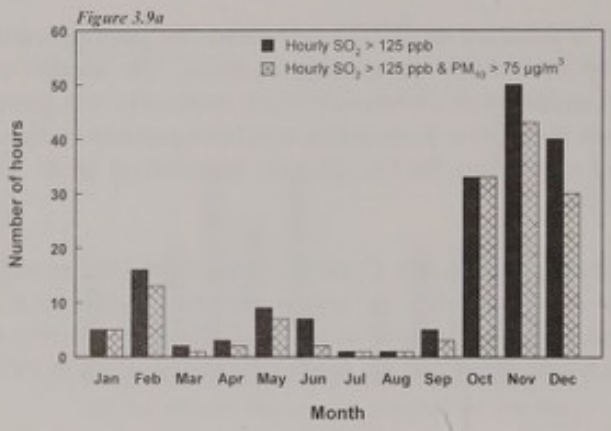
Type 2, Vehicle Smog Episodes

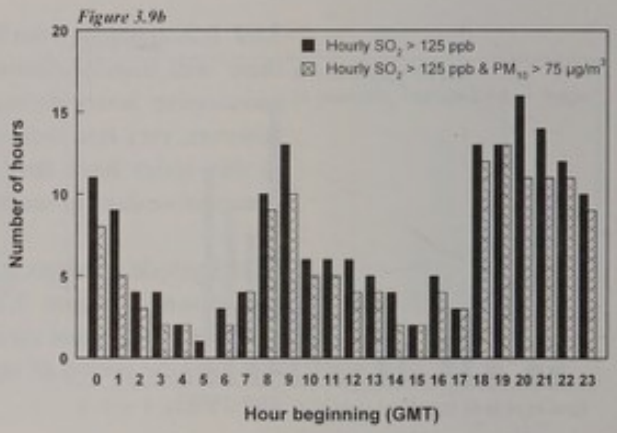
3.73 The annual and diurnal incidence of combined Type 2 NO_2/PM_{10} episodes in the urban network in 1992 and 1993 are shown in Figures 3.8a and 3.8b. Hourly average exceedences of 100 ppb (188 $\mu g/m^3$) NO_2 are graphed, together with periods when combined hourly average concentrations of NO_2 and PM_{10} exceeded 100 ppb and 75 $\mu g/m^3$ respectively (the PM_{10} threshold is used here as an arbitrary indicator of elevated particulate concentrations).

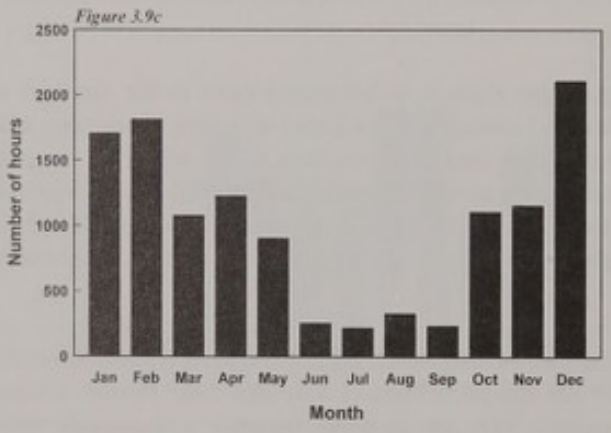
3.74 These graphs show that 56% of elevated NO_2 levels at urban sites from 1992-1993 were also associated with increased PM_{10} concentrations. Had a further vehicle-generated pollutant, CO, been included the relative incidence of combined episodes would have been higher still. This analysis provides some confidence that Figures 3.8c-3.8f, which examine NO_2 exceedences of 100 ppb in isolation, will provide meaningful information on combined Type 2 episodes.

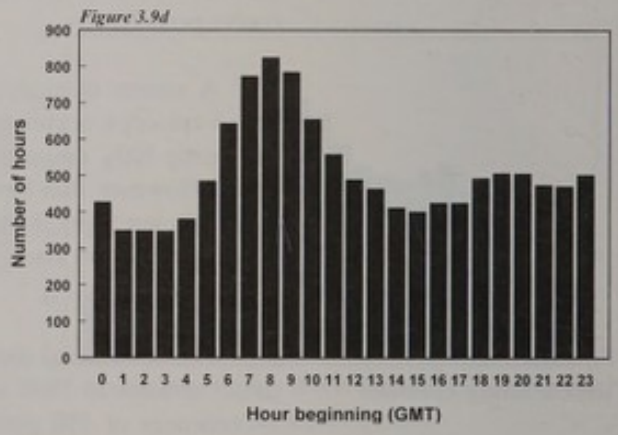
3.75 It is clear from Figure 3.8c that these episodes can occur at any time of the year from early summer to late winter. Although previously it was assumed that high NO_2 and PM_{10} levels occur only in winter, Figures 3.8a and 3.8c suggest otherwise, and indicate that combined vehicle pollutant episodes can also occur during the summer months. However, it is clear that the highest concentrations of NO_2, PM_{10} and CO occur in winter.

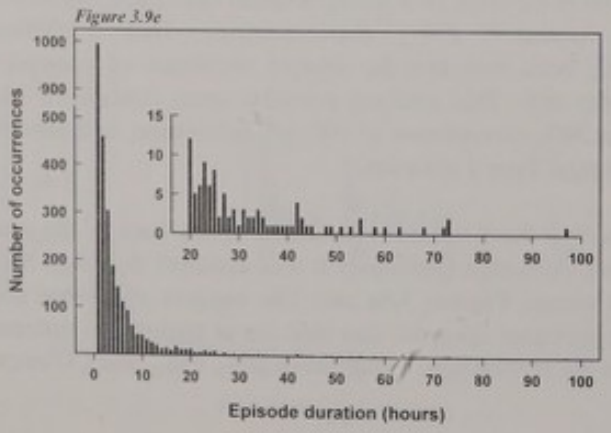
Figure 3.9 **Analysis of Type 3, winter smog, episodes. a) Monthly incidence of occasions when hourly SO_2 average concentration exceeded 125 ppb and the co-located hourly PM_{10} average concentration was greater than 75 µg/m^3, data from all urban network sites, 1992-1993; b) Diurnal incidence of the hours in which SO_2 and combined SO_2/PM_{10} episodes as defined in a) above occurred, data from all urban network sites, 1992-1993; c) Monthly incidence of episodes in which the hourly SO_2 average concentration exceeded 125 ppb, data from all available sites, 1972-1993; d) Diurnal incidence of episodes in which the hourly SO_2 average concentration exceeded 125 ppb, data from all available sites, 1972-1993; e) Duration in hours of episodes when hourly SO_2 average concentrations exceeded 125 ppb, data from all sites 1972-1993; f) Annual incidence of episodes with an hourly average concentration of SO_2 exceeding 125 ppb, data from Central London.**

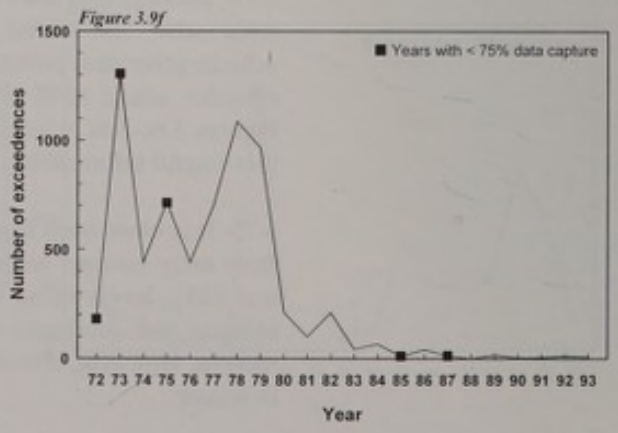












3.76 Elevated NO_2 concentrations tend to be associated with the daytime hours (see Figure 3.8d) and in particular with rush-hour periods when traffic emissions are at their highest. Episode numbers are higher during the morning rush hour, as atmospheric stability tends to be greater than during the corresponding early evening period.

3.77 Episodes typically occur for only an hour (Figure 3.8e), with the incidence of more extended episodes dropping rapidly and very few episodes lasting over 10 hours. The December 1991 episode in London, with periods of 29 and 34 consecutive hours when NO_2 concentrations exceeded 100 ppb (188 $\mu g/m^3$), is clearly exceptional in this context.[6]

3.78 Strongly fluctuating episode numbers in Central London from 1976 to 1993 are illustrated in Figure 3.8f. Despite the major extended episode in 1991, it is interesting to note that total NO_2 exceedence numbers were actually higher in 1982. There is no clear indication of a long-term trend here, and corresponding results from 1986 for NO_2 EC Directive measurement sites likewise fail to indicate any consistent changes in the incidence of Type 2 episodes over time.[10]

Type 3, Winter Smog Episodes

3.79 The majority – over 80% – of elevated SO_2 periods at urban network sites were associated with high PM_{10} concentrations (Figures 3.9a and 3.9b). Incorporating other pollutants characteristic of Type 3 episodes, such as CO or NO_2, would further increase the proportion, showing that elevated SO_2 levels are almost always associated with high concentrations of other pollutants.

3.80 By examining the SO_2 episode distributions in Figures 3.9c and 3.9d it can be seen that Type 3 episodes over the last 20 years have most frequently occurred from December to February, during the early morning hours.

3.81 These conclusions relate to a large dataset with most of the early data from London. By contrast, the more recent urban network dataset used to prepare Figures 3.9a and 3.9b provides some interesting contrasts. As previously indicated, most of these episodes were in Belfast, and it can be seen that these tend to occur from October to December, with a substantial peak in incidence during the early to late evening.

3.82 The majority of SO_2 episodes last only 1-2 hours (Figure 3.9e), with very few exceeding 10 hours in duration. A very marked downward trend in the number of Type 3 episodes in London over time exists (Figure 3.9f). This is consistent with the nationwide move towards the use of cleaner fuel for space heating, and the consequent decline in domestic emissions over the last 30 years.[11]

Overview of UK episodes types and characteristics

3.83 For convenience, the main features of UK combined pollutant episodes are summarised in Table 3.11.

Summary and conclusions

3.84 Episodes of air pollution fall into three general categories: a Type 1 summer smog, a Type 2 vehicle smog and a Type 3 winter smog. Indicator pollutants are denoted for each type of episode.

3.85 The main, or indicator, pollutant associated with the Type 1 episodes is ozone, with a contribution from nitrogen dioxide occurring in cities. The ozone is formed indirectly from pollutants emitted from vehicle exhausts, from industrial processes, or from solvents. The reactions which give rise to ozone are dependent on sunlight and high temperatures. Rural and urban areas may both be affected and the predisposition towards summer episodes means that there is the possibility of these being associated with raised levels of aeroallergens.

3.86 Nitrogen dioxide is the main pollutant associated with motor vehicle-driven, Type 2, episodes; there is also a secondary association with particles, e.g. PM_{10}. Since motor vehicles are the primary source, these episodes usually occur in urban areas. Such episodes are not restricted to any one season, but, because of their reliance on a period of calm, still weather to allow accumulation of pollutants, they tend not to occur during February and March.

3.87 Motor vehicles are also associated with Type 3 winter episodes; however, the contribution of domestic heating in certain areas of the United Kingdom results in the presence of sulphur dioxide in the pollutant mixture. Sulphur dioxide may be used as the indicator pollutant for these episodes, which are also frequently associated with elevated levels of particles (PM_{10}). As in Type 2 episodes, there is a requirement for stable meteorological conditions; in addition, the nature of the dual sources restricts these episodes to urban locations and the winter season.

Table 3.11

Characteristics of UK episodes involving combinations of air pollutants

Characteristics	Type 1 'Summer Smog'	Type 2 'Vehicle Smog'	Type 3 'Winter Smog' (mixed sources)
Major pollutants*	**O_3**, NO_2	**NO_2**, PM_{10}, CO	**SO_2**, PM_{10}, CO, NO_2
Pollutant sources	*Indirectly from:* Motor vehicles industrial processes and solvents	Motor vehicles	Motor vehicles domestic heating
Other influences	Air chemistry, long range transport, sunlight and high temperatures	*Winter:* Stable meteorology, light winds, fog, shallow mixing layer, low temperatures *Summer:* Stable meteorology, light winds, high temperatures	Stable meteorology, light winds, fog, shallow mixing layer, low temperatures
Areas affected	Rural/Urban	Urban	Urban
Main season	April-September	April-January	October-May
Likelihood of association with aeroallergens	Probable	During summer episodes	Improbable
Trends over time of concentrations of the indicator pollutant	Possible decrease in southeast England, increase in rural areas	Not apparent	Declining in most areas

*The indicator pollutant for each type of episode (see paragraph 3.60) is shown in bold type.

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Annex 3A

Concentration Units and Conversion Factors

Concentrations of air pollutants are expressed in two ways, either as the mass of pollutant in a given volume of air (usually expressed as micrograms per cubic meter or $\mu g/m^3$) or as the ratio of the volume of the gaseous pollutant (expressed as if pure) to the volume of air in which the pollutant is contained (usually expressed as a volume mixing ratio or parts per million, ppm, or parts per billion, ppb).

The mass concentration as expressed above will be dependent on the ambient temperature and pressure and ideally these should be specified each time a concentration is measured as a mass/volume. The variation is discussed below and although not large may not be negligible where large variations in temperature and pressure occur.

The volume mixing ratio is independent of temperature and pressure, if ideal gas behaviour is assumed.

The relationship between the two sets of units can be expressed as follows:

$$\mu g/m^3 = ppb \times \frac{molecular\ weight}{molecular\ volume}$$

$$where\ molecular\ volume = 22.41 \times \frac{T}{273} \times \frac{1013}{P}$$

where T is the ambient temperature (°K) and P is the atmospheric pressure (in millibars). Conversion factors for some common gaseous pollutants are given in the Table below for 20°C and 0°C and 1013 mb pressure. Pollutants which are present in particulate form in the atmosphere such as sulphates are normally only expressed in mass/volume units.

Pollutant	Molecular weight	To convert* ppb to $\mu g/m^3$		$\mu g/m^3$ to ppb	
		0°C	20°C	0°C	20°C
NO_2	46	2.05	1.91	0.49	0.52
NO	30	1.34	1.25	0.75	0.80
HNO_3	63	2.81	2.62	0.36	0.38
O_3	48	2.14	2.00	0.47	0.50
SO_2	64	2.86	2.66	0.35	0.38
CO†	28	1.25	1.16	0.80	0.86

* i.e., to convert ppb of SO_2 at 0°C to $\mu g/m^3$ multiply by 2.86

† for CO the factors apply to the more commonly used conversions of ppm and mg/m^3.

Chapter 4

Mechanistic and Toxicological Studies of Complex Pollutant Mixtures

Theoretical sequence of biochemical and cellular changes induced by complex mixtures in the respiratory tract

4.1 Full details of the repair mechanisms and the disease processes resulting from failure to repair the respiratory tract after damage by air pollutants are described in the three previous reports from this Advisory Group on 'Ozone',[1] 'Sulphur Dioxide, Acid Aerosols and Particulates',[2] and 'Oxides of Nitrogen'.[3] These may be summarised as follows.

4.2 When chemicals/particles are inhaled they react primarily with the protective biochemical secretions lining the epithelium in the nasal passages, large and small airways and alveolar regions of the respiratory tract. Thus, components of the epithelial lining fluid including mucus, antibacterial proteins and immunoproteins, low molecular weight antioxidants and pulmonary surfactant may all have an important defensive rôle in reducing the interactions between the inhaled xenobiotic and the epithelial cell surface. This extensive primary chemical defence is enhanced by the activation of cells such as macrophages and polymorphonuclear leucocytes (PMNs, neutrophils) which have phagocytic potential and the mechanical movement of this complex extracellular fluid barrier by the mucociliary escalator.

4.3 The primary defence may be breached as a result of chemical/particle overload or the generation of biologically reactive molecules (for example free radicals) formed during the extracellular chemical reactions. Epithelial defensive systems then become important, often to reduce the effects of oxidative stress and lipid peroxidation. Secretory epithelial cells (type 2 alveolar, Clara cells) seem particularly responsive to xenobiotic damage possibly because they readily accumulate chemicals or convert them *via* their complex P450 monooxygenase enzyme systems to more reactive and damaging metabolites. Other cells (*i.e.* type 1 alveolar) may be vulnerable because they have a large surface to volume ratio and poor defences against oxidative stress.

4.4 For whatever reason, chemical/particle overload leads to epithelial cell damage, lipid peroxidation and cell death. The release of inflammatory mediators and the denudation of the basement membrane of epithelia stimulates and amplifies the inflammatory cascades. The epithelial permeability barrier is compromised and fluid exudate leaks into the airway or alveolus. Such events may accompany a reduction in lung function (albeit temporarily), reduce gaseous exchange and compromise clearance and detoxification mechanisms.

4.5 In the absence of further xenobiotic exposure, progenitor epithelial cells multiply and differentiate to replace the normal surface epithelium. Continued exposure to the xenobiotic, or persistent damage to the replicating/differentiating cells, results in hyperplastic or abnormal metaplastic changes in the epithelium. These alterations are often accompanied by changes in the connective tissue underlying the epithelial basement membrane. Thus, fibroblasts are stimulated, replicate, produce more collagen and the repair process of fibrogenesis takes place.

4.6 The exact mechanisms by which the above changes become irreversible and localised areas of the lung become fibrotic or emphysematous or show signs of neoplastic change are unknown.

4.7 In summary, there are a number of stages in xenobiotic-induced lung damage/repair, some of which are reversible and others which lead to permanent disease.

Toxicological approaches to complex mixtures

The UK pollution mixture

4.8 To date no toxicological studies have been carried out on the complete mixture of chemicals/particles which may be inhaled during a UK pollution episode. The very complexity of the mixture, which may contain oxidising and reducing gases and a highly variable particulate fraction containing both organic and inorganic components (see Chapter 3 and other sources[4,5]), makes it extremely difficult to study. Some components of the reaction mixture are extremely unstable (see paragraph 4.16 below). Urban and rural episodes result in exposure to quite different mixtures. Sulphur dioxide (SO_2, a reducing gas) and sulphate-rich particles from coal combustion may be prominent components of a Type 3 episode as can occur in Belfast (see Chapter 3) whilst nitrogen dioxide (NO_2, an oxidising gas) and motor transport generated particles may be more important in a Type 2 episode occurring in London.[6] It may be speculated that the particulate fraction from episode to episode in any single city might be variable by gravimetric weight, number of particles, size distribution and chemical composition.

4.9 These variables are important in assessing health effects in that some of the major gaseous pollutants are considered to target different areas of the respiratory tract. Thus, SO_2, which is highly soluble in aqueous fluids, is mostly removed in the nasal passages. In contrast, oxidising gases (O_3 and NO_2) may react chemically with the various antioxidants to be found at different levels of the respiratory tract and yet will preferentially damage the epithelial cells of the transitional zone between the terminal bronchioles and the alveolar ducts.[3] It is in this zone that peak dose levels, in terms of mass of gas absorbed per unit area of tissue surface, occur. In addition, the severity of toxicological effect may be enhanced by particles of a size small enough to penetrate deeply into the lung. Size distribution studies of PM_{10} show that most of the particles are less than 1 micron (μm) in diameter. Many of these may be in the 10-100 nanometer (nm) range and, depending on their surface characteristics, may be able to penetrate the epithelium and become deposited in the interstitium (see paragraph 4.12 below). Ultrafine particles of 20 nm diameter have a 50% deposition efficiency in the alveolar region of the lung. A further complication is the potentially variable nature of the surface chemistry of the particle once it enters the respiratory tract. Thus, pure carbon particles (for example the soot component of diesel exhaust) would be expected to produce a different toxicological effect from that of the same particles onto which are adsorbed hydrocarbons, or the same carbon particles carrying or containing sulphates and heavy metals or acidic, basic, aromatic or oxygenated compounds (other components of fossil fuel combustion).

4.10 It is issues of this nature that can be addressed in the long term by the toxicologist who, for the most part, has concentrated on the effects of individual pollutant components mostly restricted to *in vitro* investigations or studies with experimental animals. The approach of the toxicologist to studying mixtures has been reviewed recently in two articles.[7,8] There are three commonly considered interactions between two (or more) agents in a mixture which produce measurable effects following exposure:[8]

- *Additive*: when the combined effects of the two (or more) agents *equals* the sum of the individual effects;
- *Synergistic*: when the combined effect of the two (or more) agents given together *exceeds* the sum of the effects of the agents given singly; and
- *Antagonistic*: when the combined effect of two (or more) agents given together *is less than* the sum of the effects of the agents given singly.

Toxicological studies with complex mixtures in experimental animals

Urban pollution mixtures, urban particles and acid fogs

4.11 Two recent studies have reported the effects of urban pollutants on alterations in the respiratory tract[9] and on the pathology of nasal passages[10] in the same groups of rats. One group of rats was maintained for 6 months in a "polluted" environment of downtown São Paulo, Brazil. A second group of rats was maintained in a "clean" environment in a rural area 50 km from São Paulo. The authors reported significant differences in the "polluted" group with respect to (a) nasal resistance, (b) a slight increase in nasal epithelial volume, (c) increased acidic and neutral mucus in the trachea and bronchi attributed to secretory hyperplasia, (d) a small increase in white cell number (but not macrophages) in bronchoalveolar lavage fluid and (e) abnormal cilia being "frequently" seen. No significant differences were reported between lung resistance measurements in

"polluted" and "clean" groups. Of some concern is that 37 out of 69 (54%) of the "polluted" group and 10 out of 56 (18%) of the "clean" group died during the exposure period. The former death rate is exceptionally high and was attributed to a *Mycoplasma* infection which, in itself, may account for some of the changes attributed to the pollutants.

4.12 Jimba *et al.*[11] have instilled respirable urban particles, collected from Kingston, Tennessee, USA into the lungs of hamsters (600 µg/100g body weight) and have shown that 24 hours later significant increases had occurred in components of bronchoalveolar lavage fluid: albumin (a permeability marker, × 5), lactate dehydrogenase (a non-specific marker of cell damage, × 2.3), ß-*N*-acetyl-glucosaminidase (lysosomal enzyme, × 2.2) and polymorphonuclear leucocytes (× 12). The authors concluded that urban particles could produce cell injury and inflammation, which was exacerbated in exercising animals. Interestingly, they also reported that these measured parameters had returned to normal levels when animals were examined on day 7. It would seem to be important to establish whether any other lung changes could be noted at this 7-day time when perhaps the primary inflammatory response was complete. It is unfortunate that the size distribution and chemical composition of these urban particles are not recorded, in that correlations could be made with the 'uncoated' model particles such as titanium dioxide (TiO_2), gallium sesquioxide (Ga_2O_3), and carbon black used by other investigators.[12] Oberdörster *et al.* drew attention[12] to a number of studies which have shown that (a) 200 nm diameter TiO_2 particles cross the alveolar barrier in increasing amounts once the lung burden of the rat has reached 1 mg, whereas at lower doses the alveolar macrophages contain most of the particles; (b) 20 nm diameter TiO_2 particles, when inhaled by rats, are readily detected in the interstitium and interstitial macrophages; (c) Ga_2O_3 particles of approximately 14 nm diameter are highly toxic and fibrogenic when inhaled by rats and yet the same mineral of particle size greater than 6 µm does not produce these effects. Oberdörster and colleagues showed that instillation of 20 nm (ultrafine) TiO_2 particles (500 µg) into the lungs of rats was associated with a high retention of particles within the interstitium and/or the epithelium and was accompanied by a significant inflammatory reaction at 24 hours.[12] Such an effect was not detected with 200 nm diameter particles, of which far fewer accumulated in the epithelium/interstitium. The same authors had reported that ultrafine aluminium oxide (Al_2O_3), but not ultrafine carbon black, also readily penetrates the epithelium, and therefore suggested that size alone is not the only criterion and that inorganic composition of the particles may also be important[12] Collectively these data, albeit derived from short term studies, indicate that during particle overload ultrafine particles more readily penetrate the epithelium and more readily exacerbate the inflammatory response, perhaps bypassing the protective alveolar space macrophage clearance system. (This topic is covered in more detail in a report currently in press.[13])

4.13 The conclusions of Oberdörster and his coworkers have been summarised by Lippmann as follows:[14]

'
- the delivered dose rate of particles to the lung is a determinant of the acute inflammatory PMN [polymorphonuclear leucocytes] response,
- the process of phagocytosis of "nuisance" particles by AMs [alveolar macrophages], rather than the interstitial access of the particles, appears to initiate the influx of PMN into the alveolar space,
- the surface area of the retained particles correlates best with inflammatory parameters rather than the phagocytized particle numbers, mass, or volume,
- Interstitialization of particles appears to be important for inducing inflammatory responses including the induction of fibrotic reactions, and
- If the interstitialized particle fraction exceeds the particle fraction remaining in the alveolar space, the influx of PMN into the alveolar lumen decreases, conceivably reflecting a reversal of chemotactic gradients from alveolar space toward the interstitial space.'

4.14 It is still unclear if (ultrafine) urban particles of variable inorganic composition, with variable surface organic molecules and in mixtures containing other primary (CO, NO, NO_X, SO_2) or secondary (O_3, NO_2, acids) pollutants would behave in a similar manner to the model compounds. However, studies have shown the long term retention of particulate material in the lung parenchyma of non-smoking, non-occupationally exposed human subjects to be highly variable.[15] This author reported that there is a statistically significant correlation between age and the extent of particle accumulation but, whilst the lungs of some individuals had no pigmentation due to particles, in others as much as 8 to 12 percent of the parenchyma was accounted for by particulate material. The author concluded that (a) this variability was most likely due to differences in effective clearance rather than to life long differences in ambient exposure to particles and (b) the variation in dust accumulation would mean that some individuals will be far less susceptible than others to the effects of toxic atmospheric particles. The retention of particles by the lung is often underestimated. Churg has shown that the typical particle burden of the lung parenchyma may be of the order of 10^7 to 10^8 particles per gram of dry tissue. As Churg has further pointed out, this is, in numerical terms, a very considerable burden but one which seems to be tolerated without causing dust-related disease.[16]

4.15 Mautz *et al.*[17] found that when rats were exposed for 4 hours to components of acid fogs (without particles) containing O_3 (400 ppb, 800 $\mu g/m^3$) plus nitric acid (0.7 mg/m^3) and sulphuric acid (0.6 mg/m^3) then nasal epithelial injury, lung parenchymal lesions or lavage protein levels were no different than when animals were exposed to O_3 alone (400 ppb, 800 $\mu g/m^3$). Thus, the toxic effects of O_3 predominated and no synergistic or additive effect with the inhaled acids were found. Furthermore, these investigators found no synergism between O_3 and hydroxymethanesulphonic acid (HMSA), a common component of California fogs produced by interaction between bisulphite and formaldehyde. Earlier studies[18] showed that high levels of HMSA did not produce bronchoconstriction in asthmatic subjects.

Diesel and gasoline exhaust mixtures

4.16 Diesel and gasoline (petrol) combustion by vehicles account for some 27% of the UK PM_{10} source inventory,[5,19] in addition to supplying chemicals important for the generation of secondary pollutants. Experimental studies with these complex mixtures have been reviewed by Mauderly.[8] One of the earliest large scale studies is that of Hueter *et al.*[20] who exposed mice (n=2016), rats (n=126), hamsters (n=72) and guinea pigs (n=99) to irradiated (to generate photochemical pollutants) or nonirradiated (raw) auto exhaust for periods of 6 weeks to 23 months. The concentration of the irradiated exhaust mixture in the exposure atmosphere was varied to contain between 20-100 ppm (23-115 mg/m^3) CO, 200-1000 ppb (400-2000 $\mu g/m^3$) O_3, 400-2000 ppb (500-2500 $\mu g/m^3$) NO, 300-1900 ppb (564-3570 $\mu g/m^3$) of NO_2 and 6-36 ppm total hydrocarbon. Ozone and NO_2 are absent in the raw exhaust and the composition of the hydrocarbon fraction is different. These authors noted the high reactivity and chemical instability of many of the exhaust components in that some 85% O_3, 12% NO and up to 60% of the NO_2 were lost during passage through the animal chambers. No significantly different effects of the auto exhaust were noted with respect to animal mortality, morbidity, growth, immunology, blood gas analysis or oxygen consumption. The reported pathological changes in the different strains of mice induced by auto exhaust exposure are difficult to ascertain. All strains, but particularly the A/j strain, developed amyloidosis (complex protein deposition) in organs other than lung, whereas the C_{57}/B strain was more prone to pulmonary inflammation, "bronchitis" and pneumonia. A positive correlation was found between all exposures and the presence of dark particle accumulation in macrophages. Increases in dried lung weight and decreases in lung lipids were also noted in exposed rats. Lewis *et al.*[21] reported no effects on pulmonary function after 18 or 36 months exposure of dogs to autoexhaust (with and without NO_2 and SO_2) for 16 hours/day, 7 days/week. After 61 months exposure, lung volumes, compliances and maximum breathing capacity were not impaired by the experimental procedures. However, at 61 months, raw exhaust plus oxides of sulphur produced pulmonary hyperinflation and increased expiratory resistance.

4.17 Studies by Mauderly *et al.*[22] have shown that rats exposed during lung development to diesel exhaust (or NO_2) were not more susceptible to changes in lung function than adult animals. Rats were exposed to whole diesel exhaust at the high concentrations of 3.5 mg/m^3 total particles, 7.9 ppm CO (9.1 mg/m^3), 4.7 ppm hydrocarbons and 5 ppm NO_2 (9.4 mg/m^3) for 7 hours/day, 5 days/week for 6 months and examined for changes in respiratory function, lung burdens and clearance of particles, biochemical parameters in airway fluid and lung and histopathology. Diesel exhaust altered airway fluid components and slightly increased lung collagen (10-12%) at the end of the 6 month exposure period in both developing and adult rats. In addition, the exposed adults had a significantly higher lung/body weight ratio than did the control rats. The soot burden in developing and adult animals was similar at the end of exposure but, in a six month recovery period, the adults showed little or no reduction in this burden whereas the developing animals did show some clearance. These latter two observations may suggest that adult animals are more affected by diesel exhaust and less able to recover than younger, developing animals.

4.18 Brightwell *et al.*[23] have reported a detailed study in which rats and hamsters were exposed for up to 2 years (16 hours/day, 5 days/week) to emissions from (a) a gasoline engine; (b) a gasoline engine fitted with a catalytic converter; (c) a diesel engine; and (d) a diesel engine attached to a filtration system which removed 99.97% of the particles (filtered diesel). The exposure regimes and the components present in the mixtures are shown in Table 4.1, together with some of the observed biological effects. Rats exposed to the gasoline mixtures or filtered diesel emissions showed no increase in lung tumours over those observed in control animals. In contrast, rats exposed to diesel emission showed a dose-dependent increase in tumours which was significant in the medium and high exposure groups. After 24 months of exposure the tumour incidence was particularly high in female rats (96%, of which 77% were malignant tumours). This may be explained by the fact that female rats have a lower lung/body weight ratio than males and thus the xenobiotic burden could be higher. The authors concluded that the apparent carcinogenic effect observed with diesel exhaust is probably associated with the presence of high concentrations of soot particles. Coupled with the carcinogenic effect of the diesel exhaust it is noteworthy that other biological changes also occurred, such as a reduced body weight (noted after 12 months exposure) and an increase in lung weight (noted as early as 6 months after exposure). With the exception of the high dose of gasoline exhaust the rats exposed to relatively high concentrations of CO, NO, NO_X and hydrocarbons showed no change in body weight from control animals. Brightwell and colleagues pointed out that the significant carcinogenic effect produced with the diesel emission required a particle concentration of 2200 µg/m^3, whereas, in cities of the USA, the mean concentration of soot particles is estimated to be 0.5 µg/m^3 (this very low level is explained by the low use of diesel-powered vehicles in urban areas of the USA, in contrast to the situation in the UK and Europe). This difference implies a safety margin of some orders of magnitude in the potential effects on humans but extrapolation from animal studies to humans with respect to dose is difficult (see paragraph 4.24 below).

Oxidant gas mixtures

4.19 The majority of studies have been carried out with sequential or combination exposures of NO_2 and O_3 in rodents (mainly rats) and are summarised in Table 4.2. All of the studies described relate to damage of a biochemical or cellular nature which is potentially reversible. Thus, events such as lipid peroxidation, the depletion of antioxidant status, an increase in epithelial permeability and a mild inflammatory reaction involving PMNs would be expected to be rapidly corrected. If focal damage occurred to parts of the epithelial lining layer then progenitor epithelial cells would be expected to divide and rapidly replace the barrier. From the studies described on O_3/NO_2 exposures there is no information as to whether recovery is delayed or, indeed, does not occur. Most of the investigators reported that combined exposures to O_3/NO_2 produce synergistic effects. Interestingly, in the more detailed studies, sequential exposures to the oxidising gases usually only produce additive effects,[24] although the measured endpoint of toxicity and the species exposed may also be important in this regard.[24,25] Of note is that oxidising gas exposures do not seem to produce any antagonistic effects. Gelzleichter and colleagues reported that the synergistic effects of O_3 and NO_2 on lavage protein or epithelial cells in this fluid would be unlikely in environmental or occupational settings.

Table 4.1

Biological effects of motor vehicle exhausts on Fischer 344 rats, from Brightwell *et al.*[23,38]

Exposure exhaust	Concentration	Mixture composition (mean values) CO (ppm)	NO_x* (ppm)	NO * (ppm)	Total hydrocarbons (ppm)	Particles (mg/m^3) **	Biological effects Reduced body weight	Impaired respiratory efficiency	Increased lung weight	Number of primary lung tumours	Tumour incidence after 24 months
Gasoline (petrol)	M	67	15	15	20	nd	×	×	×	1/76	
	H	224	49	44	61	nd	✓	×	×	1/128	
Gasoline + catalytic converter	M	6	2	2	2	nd	×	×	×	0/73	
	H	21	7	6	3	nd	×	×	×	1/129	
Diesel	L	3	0.9	0.7	3	0.7	✓	✓	×	1/143	
	M	9	2.7	2.1	6	2.2	✓	✓	✓	14/144	♀ 43% ♂ 8%
	H	32	8	6	17	6.6	✓	✓	✓	55/143	♀ 96% ♂ 44%
Filtered diesel	M	10	2.8	2.2	7	nd	×	×	×	0/144	
	H	32	8	7	16	nd	×	×	×	0/143	
Control ***		1	0.1	0.1	2	nd				3/260	

*Difference between NO_x and NO = NO_2 concentration

**Lower limit of detection = 0.21 mg/m^3 with 33% loss of particle mass before entering the exposure chamber

***Conditioned air

The rats were housed in inhalation chambers for the duration of the exposure phase of the experiment. They had access to food and water *ad libitum*. Exposures were for 16 hours per day, 5 days per week, for 2 years. Exposures L = low; M = medium; H = high; nd = not detected; × = not different from controls; ✓ = significantly different from controls (Dunnett's *t*-test specified for body weight differences, otherwise no details).

Conversion factors:

1 ppm NO	=	1.25 mg/m^3
1 ppm NO_2	=	1.88 mg/m^3
1 ppm CO	=	1.15 mg/m^3

This is because synergistic toxicological reactions have only been detected with high (experimental) concentrations of O_3 and NO_2 and such synergism may well be a result of the formation of nitrogen pentoxide (N_2O_5).[24]

4.20 A long term study in rats treated with a carcinogen, *N*-bis (2-hydroxypropyl)-nitrosamine (BHPN), indicated that animals exposed to low combinations of NO_2 and O_3 for 13 months developed more lung tumours (incidence 13.9%) than animals treated with BHPN and O_3 alone (incidence 8.3%).[26] Animals treated with BHPN alone or those exposed to the combinations of NO_2/O_3 alone did not develop any lung tumours. This could suggest a tumour promoter activity for O_3 which is enhanced in the presence of a second oxidising gas.

Oxidant and acid mixtures

4.21 Combined exposures of NO_2 or O_3 and sulphuric acid produce synergistic effects with respect to elevation of lavage protein and collagen synthesis[25,27] (see also Table 4.2). In contrast, other investigators report an antagonistic effect for changes in lavage protein in combined exposures of nitric acid and O_3.[28] A spectrum of synergistic, additive or null effects are reported in rabbits or tissue derived from the animals exposed to sulphuric acid/O_3 combinations (Table 4.2). As mentioned previously, the nature of the toxic effect may be assay specific. Even more confusing is that, for the same assay system (*in vitro* bronchial ring hyperreactivity), low doses of O_3 (100 ppb, 200 $\mu g/m^3$) may be antagonistic whereas higher levels (300 ppb, 600 $\mu g/m^3$) may be synergistic when combined with exposure to sulphuric acid.[29]

Oxidants, acids and particles

4.22 The majority of studies reported employ sequential exposures, either firstly to the oxidant gas and then subsequently to particles (or acid plus particles) or *vice versa* (see

Table 4.2

Effects of combinations of chemical pollutants on the respiratory tract of animal species

Author(s)	Chemical combinations	Dose	Exposure period	Species	Comments	Pollutant with predominant effect, where known
Sagai *et al.* (1987),[39]	NO_2	0.4 ppm	2 weeks	Mice	Species differences in response. Synergistic reactions for lipid peroxidation and antioxidant status.	
	+			Rats		
Ichinose and Sagai (1989)[40]	O_3	400 ppb		Hamsters		
				Guinea		
Takahashi and Miura (1989)[41]	NO_2	4 ppm	1-2 months	Rats	Increase in P-450 monooxygenase activity induced by O^3 alone is lowered by combined exposure to NO_2.	O_3
	+					
	O_3	200 ppb				
Lee *et al.* (1989)[42]	NO_2	1.8 ppm	3 days	Rats	Combined exposure synergistic for increase O_3 lung glucose-6-phosphate dehydrogenase, glutathione perioxidase and disulphide transhydrogenase activities. Additive for other enzymes.	
	+					
	O_3	450 ppb				
Mautz *et al.* (1988)[43]	NO_2	0.6/2.5 ppm	3-4 hours	Rats	Combined exposures synergistic with respect to increased lesions in lung parenchyma.	
	+					
	O_3	350/600 ppb				
Sagai and Ichinose (1991)[44]	NO_2	0.4-4 ppm	22 months	Rats	Combined exposures synergistic for increase in lipid preoxidation.	
	+					
	O_3	50 ppb				
Gelzleichter *et al.* (1992)[24]	NO_2	3.6-14.1 ppm	3 days	Rats	Combination exposures produce synergistic effects. Sequential exposures produce additive effects. Increases noted in lavage protein, epithelial cells and PMNs. Threshold levels for synergy not encountered in environmental exposures.	O_3?
	+					
	O_3	200-800 ppb				
Elsayed (1994)[45]	NO_2	1.8 ppm	3 days	Rats	Synergism with respect to stimulation of polyamine biosynthesis and DNA synthesis in lung.	NO_2?
	+					
	O_3	450 ppb				
Rajini *et al.* (1993)[46]	NO_2	3.6-14.4 ppm	3 days	Rats	Synergism, particularly at high dose combinations, with respect to an increase in airway and alveolar epithelial proliferation.	NO_2?
	+					
	O_3	200-800 ppb				
Umezu *et al.* (1993)[47]	NO_2	4-12 ppm	2-7 days	Mice	Suppression of drinking activity and body weight loss with individual oxidant exposures. Animals exposed to NO_2 (12 ppm, 7 days) are tolerant to a sequential exposure to O_3.	
	+					
	O_3	100-800 ppb				
Ichinose and Sagai (1992)[26]	NO_2	0.4 ppm	13 months	Rats	Chemically-induced lung tumours show a slightly higher incidence for O_3/NO_2 than for O_3 alone or NO_2/H_2SO_4.	
	+					
	O_3	50 ppb				
	or					
	H_2SO_4	1 mg/m^3				

Table 4.2 (continued)
Effects of combinations of chemical pollutants on the respiratory tract of animal species

Author(s)	Chemical combinations	Dose	Exposure period	Species	Comments	Pollutant with predominant effect, where known
Lee *et al.* (1992)[48]	NO_2 + O_3 + H_2SO_4	1.8 ppm 450 ppb 1 mg/m^3	3 days	Rats	Ozone effects on antioxidant defences and lung inflammatory responses are potentiated by NO_2 and H_2SO_4	
Last and Warren (1987)[27]	NO_2 + H_2SO_4	5 ppm 1 mg/m^3	1-7 days	Rats	Combined exposure synergistic for elevated lavage protein and collagen synthesis	
Mautz *et al.* (1988)[43]	HCHO + O_3	10 ppm 600 ppb.	3-4 hours	Rats	Antagonism for combined exposure on lung parenchymal damage compared with O_3 alone. Nasal epithelial changes primarily due to HCHO but enhanced by O_3	
Nadziejko *et al.* (1992)[28]	HNO_3 + O_3	1 mg/m^3 600 ppb	4 hours	Rats	Combined exposure antiagonistic for lavage fluid protein elastase inhibitory capacity and % 'free' neutrophils. Effects additive for macrophage respiratory burst activity, production of LTC_4 and % 'free' macrophages.	
El-Fawal *et al.* (1992)[29]	H_2SO_4 + O_3	74 µg/m^3 100-600 ppb	3 hours/day for up to 5 days	Rabbits	Combined exposures produce synergism for hyperreactivity measured in bronchial rings *in vitro* where O_3, exceeds 300 ppb. Antagonistic effects at 100 ppb O_3	
Schlesinger *et al.* (1992)[49]	H_2SO_4 + O_3	50-125 µg/m^3 100-600 ppb	3 hours	Rabbits	Combined mixtures produce no significant efects on lavage cell number, viability or extracellular enzymes/inflammatory mediators. Antagonism for phagocytic indices and superoxide production. Synergism for TNF-induced macrophage toxicity for 125 µg/m^3 H_2SO_4 and > 300 ppb O_3.	
Last (1991)[25]	H_2SO_4 + O_3	5-100 µg/m^3 120-640 ppb	Variable	Rats	Combined exposure when O_3 exceeds 200 ppb and H_2SO_4 100-200 mg/m^3 produce synergism with respect to lavage protein and collagen synthesis.	O_3
Pinkerton *et al.* (1993)[33]	H_2SO_4 + O_3 + particles	100 µg/m^3 120-200 ppb ?	90 days 90 days 2 hours	Rats	Greater lung retention of particles when exposed to O_3 alone or O_3/acid combination.	O_3

Table 4.2 (continued)

Effects of combinations of chemical pollutants on the respiratory tract of animal species

Author(s)	Chemical combinations	Dose	Exposure period	Species	Comments	Pollutant with predominant effect, where known
Chen *et al.* (1991)[34]	H_2SO_4	300 µg/m³	1 hour	Guinea pigs	Synergistic effect with sequential exposure of H_2SO_4 then O_3 in reducing lung diffusion capacity	Zn?
	or		recovery			
	H_2SO_4	24-84 µg/m³	then			
	on		1 hour			
	ZnO ultrafine particles	7 mg/m³				
	+					
	O_3	150 ppb				
Jakab and Hemenway (1994)[30]	O_3	1500 ppb	4 hours	Mice	Combined exposures, but not sequential, produce synergism in reducing free cell numbers, proportionately increasing PMN's and reduction in macrophage phagocytic index.	O_3
	+					
	carbon black particles	100 mg/m³				
Klingebiel *et al.* (1993)[31]	O_3	500 ppb	?	Rats	Instilled soot (500 µg) elevates lavage phospholipids and SP-A. Ozone has no effect. With combined exposures airway enzymes and proteins are increased	Soot
	+					
	soot particles	0.5-1 mg				
Pinkerton *et al.* (1989)[32]	O_3	600 ppb	6 weeks	Rats	One month after asbestos exposure significantly greater retention of mineral in lungs exposed to O_3	
	+	(+ spike)				
	asbestos	8.7 mg/m³	5 hours			
Vetrano *et al.* (1992)[33]	NO_2	20 ppm	2 hours	Mice	Decrease in lavage neutrophils and lung collagen content	Quartz
	+					
	quartz	2 mg				
Nishikawa *et al.* (1992)[35]	O_3	1000 ppb	90 min	Guinea pigs	Combined exposure increases airway responsiveness (AR) and tracheal vascular permeability (TVP).	O_3 (TVP)
	+					Smoke (AR)
	cigarette smoke	5 or 10 puffs	30 min			

Abbreviations: P-450, Cytochrome P-450; PMN, polymorphonuclear cells; HCHO, formaldehyde; LTC_4, leucotriene C_4; TNF, tumour necrosis factor; SP-A, surfactant-associated protein A; AR, airway responsiveness; TVP, tracheal vascular permeability.

Conversion factors 1 ppb NO_2 = 1.88 µg/m³
1 ppb O_3 = 2.00 µg/m³
1 ppb SO_2 = 2.86 µg/m³
1 ppb HNO_3 = 2.62 µg/m³

Table 4.2). In one study,[30] combined exposure for 4 hours to O_3 (a high concentration of 1500 ppb, 3000 $\mu g/m^3$) and carbon black particles (mass median diameter 2.4 μm) produced synergistic effects on the free cell population found in lavage fluid, whereas sequential exposures did not. This does suggest potentiation of damage with combined exposures, an effect also reported in a second study[31] and previously with the combined oxidant gases. It is possible that potentiation of damage when particles are present relates to the fact that clearance is impaired in studies utilising either sequential exposures or co-exposures with other pollutants. At least two of the studies summarised in Table 4.2 report that particle retention is greater in the lungs if animals are also exposed to O_3 or O_3/acid mixtures.[32,33] The effects of SO_2 on ciliary function were considered in the second report of the Advisory Group.[2]

4.23 Reference has already been made to the effects produced in animal species exposed to a variety of combinations of sulphuric acid, SO_2 and particles (sections 4.57 to 4.62 of reference 2). From these studies it was concluded that reversible changes in lung permeability occur following exposure to SO_2 and large concentrations of inhaled ultrafine zinc oxide (ZnO) particles (diameter < 0.1 μm). Such conclusions equate well with the studies of Jimba *et al.*[11] described above. Similar extended studies are reported by Chen *et al.*[34] (see Table 4.2) in which sequential exposure of first sulphuric acid deposited on ZnO followed by O_3 results in a synergistic reduction in lung diffusing capacity. It was previously surmised that the release of the metal ion (Zn^{++}) from the insoluble ZnO by the action of sulphuric acid might explain this damaging effect in the lung. It is interesting to note that this reversible effect can be potentiated by subsequent exposure to low levels of O_3.

Risk assessment, extrapolation from animals to humans

4.24 There are a number of difficulties when trying to apply toxicological data obtained from species of laboratory animals in attempts to predict effects in humans. Such an extrapolation is particularly difficult in respiratory toxicology because of the diversity of cellular targets for xenobiotics and the considerable interspecies variation in biotransformation potential. We are still in the unenviable position of not understanding, for *any* species, the full protective mechanisms that operate or the manner in which a target cell accumulates and metabolises any one air pollutant, let alone a complex mixture of pollutants. There is, however, a better understanding of the manner in which 'overload' doses of pollutants will produce defined toxic endpoints, such as: reduction in clearance or lung function, increased epithelial permeability or inflammation and pulmonary fibrosis, emphysema or tumour formation. The majority of this information has been derived from toxicological studies in laboratory rodents for which the concentration of toxicant and duration of exposure (the effective dose) is known. Although humans may suffer the same effects, extrapolation of the dose required to produce the same endpoint is a matter of subjective assessment. This is because rats and humans inhale materials differently (the rat is an obligate nasal breather). Rats and humans have differences in gross morphology of the respiratory tract, target cell distribution and antioxidants in the protective lining fluid which provide the first molecules to react with at least some inhaled pollutants. Rats and humans also differ in their spectrum of biotransformation enzymes which can determine the rate at which toxic compounds are degraded and removed. In the limited studies that have been carried out, human subjects always show a wider variation in biotransformation potential, antioxidant status, lung function and clearance mechanisms than a standard 'clean' laboratory rodent, which lives in a protected environment and is usually free of infection. Thus, human susceptibility to pollutants may be different from the laboratory species and the sensitivity of individual humans may vary more widely than that of the laboratory animals. In addition, susceptibility in humans may alter with health status, diet, life style and medication, confounders which are usually controlled in animal experiments. These differences perhaps explain why extrapolation of dose effects from laboratory animals to man is difficult. This topic is reviewed elsewhere.[35-37] Risk assessment is usually confined to studies with single xenobiotics and, as such, is not readily adapted to the low dose and intermittent exposures of humans to a mixture of pollutants. It would probably be accepted that, in making risk assessments, scientists can no longer look only at toxicological endpoints and that a better understanding of the mechanisms of damage and interspecies differences is required.

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Chapter 5

Air Pollution and Aeroallergens

Introduction

5.1 The presence of aeroallergens in the atmosphere has been shown to be associated both with occasional severe outbreaks of asthma involving large increases in morbidity, and with day-to-day variation in symptom severity among asthmatics and individuals with allergen-related conditions such as hayfever. Annex 5A provides more detailed descriptions of the physiological and immunological responses of sensitised individuals to inhaled allergens. The presence of air pollutants could exacerbate the severity of the symptom response to a given level of allergen exposure in atopic individuals, and thus the evidence for effects of combined, or sequential, exposure to air pollutants and aeroallergens is considered in this chapter. It should be noted that this is a different issue from that of whether air pollutants are associated with an increase in the prevalence of such conditions. However, some recent studies (*e.g.* Peat *et al.* 1994[1]) which show an increase in the prevalence of hayfever and asthma, without an associated increase in the prevalence of atopy, suggest that there may be some association between the two diseases and air pollution. This problem will be addressed in more detail in a forthcoming report.[2]

5.2 The common United Kingdom (UK) outdoor aeroallergens are grass and tree pollens, and fungal spores. The size of pollen grains depends on the species, but most are in the range 20-50 µm (typical grass pollen grains are about 30 µm in diameter). Thus, while they may be associated with nasal symptoms, they are unlikely to penetrate into the lower respiratory tract. Fungal spores are smaller, typically 5-10 µm, and thus are more respirable. However, the atmosphere may also contain fragments of pollen grains, 5 µm or less in size, which have also been shown to have allergenic activity.

5.3 In general, grass pollen levels in the UK atmosphere have tended to decline over the past 30 years, due to changes in land management and reductions in the area of grassland. However, this trend may be reversed with set-aside of fields previously devoted to cereal production. Current policies also favour an increase in woodland, while changes in agricultural policy and climatic warming may introduce new aeroallergens to the UK. Thus, it is possible that there will be a trend of increasing outdoor aeroallergen levels over the coming decades.

Co-occurrence of air pollution and aeroallergens

5.4 Before considering the evidence of combined effects of allergens and air pollutants on human health, and the mechanisms involved, it is important to consider the likely patterns of exposure, or co-exposure, of individuals to high levels of both pollutants and aeroallergens. Because this report is focused on the health effects of air pollution episodes, the analysis will concentrate on assessing whether these are associated with high concentrations of aeroallergens, rather than on examining the patterns of aeroallergen exposure in great detail.

5.5 The levels of both pollutants and of aeroallergens in the atmosphere are controlled by similar factors:

- *Rates of emission/production*. Concentrations are generally higher when and where the rates of emission into the atmosphere are raised;

- *Dispersal and deposition*. The rate of removal of the pollutant/aeroallergen will largely determine how widely it is dispersed. Thus pollutants with a high rate of deposition, such as ammonia, have a very localised distribution. Similarly for pollens: heavy pollens, such as those of many tree species, are rapidly deposited and often show localised distributions;[3] in contrast, the smaller pollens of grass species can travel greater distances and tend to be more widely dispersed;

- *Meteorological conditions*. Climatic conditions play a key rôle both in the dispersal of aeroallergens, and in their release into the atmosphere.

5.6 Given these similarities in the types of factors influencing their levels in the atmosphere, it is reasonable to assume that there will be some associations, both positive and negative, between levels of air pollutants and aeroallergens in the atmosphere. The following sections provide an outline of some of the key features, drawing both on general principles and on analysis of UK data.

Seasonal exposure patterns

5.7 Both air pollutants and aeroallergens show characteristic patterns of seasonal prevalence. Thus, high concentrations of ozone (O_3) and other photochemical pollutants are largely confined to the summer months, whereas the highest concentrations of pollutants such as sulphur dioxide (SO_2) and carbon monoxide (CO) tend to occur in winter (see Chapter 3).

5.8 A generalised aeroallergen calendar for the UK is illustrated in Figure 5.1.[4] The early spring is dominated by the tree pollens, particularly birch (*Betula*) and plane (*Platanus*), while grass pollens are at their highest levels in June and July. Nettle pollen is present later in the summer, whilst the peak months for fungal spores are generally in late summer, but can extend into the autumn. However, it should be noted that these are general patterns, and that there is considerable inter-year variation in the timing and size of the peaks for different aeroallergens.

5.9 Thus aeroallergens are less likely to be present in significant levels in winter smog episodes than in summer episodes. Episodes of elevated O_3 concentrations can occur through the months of May to September, and are more likely to be associated with higher aeroallergen levels, although the type of aeroallergen present will depend on the timing of the pollution episode.

Spatial exposure patterns

5.10 As with primary air pollutants, the spatial distribution of aeroallergens is largely determined by the location of the source, the amount of emissions and the extent to which these emissions are dispersed and transported in the atmosphere.

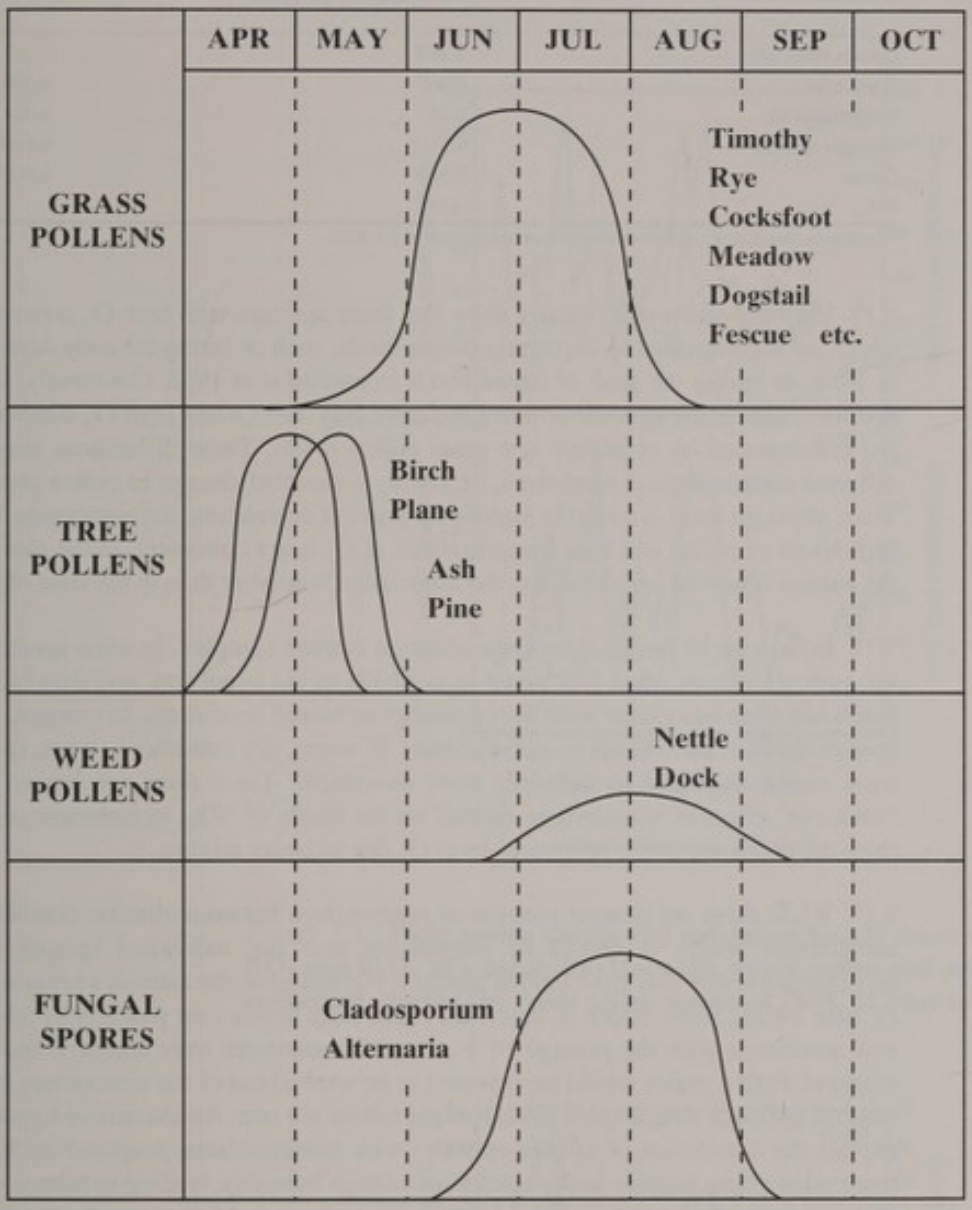
5.11 In general, exposure to aeroallergens is greatest in rural areas where the sources of grass pollen are concentrated. Indeed, urban grass pollen levels can be lower than those in surrounding areas by a factor of 2-5 on the same day. Grass pollen levels are also higher in those rural areas in which grassland is the dominant land use, such as central and western England, and are lower in upland areas. Comparing these spatial patterns with those of the major air pollutants, it is clear that there is considerable overlap between the area with high grass pollen levels and that with a high frequency of ozone episodes;[5] fewer episodes occur in urban areas and in northern Britain. In contrast, higher concentrations of pollutants such as nitrogen dioxide (NO_2), SO_2 and CO are found during urban air pollution episodes.

5.12 For tree pollens the situation is more complex, as there may be localised high urban concentrations close to trees. In the case of fungal spores, some will tend to be more common in agricultural areas or forests because of the typical host plants of the fungi, but the situation will be specific to individual fungal species.

5.13 There is also geographical variation in the seasonal pattern of aeroallergen prevalence. Thus, the onset of flowering and pollen production is delayed in colder climates: the start of the hayfever season may be 3-4 weeks earlier in southwest England than in northwest Scotland, with the season being correspondingly shorter in these cooler areas. However, the extent of this spatial variation will depend on the specific climatic conditions in individual years. Thus, photochemical episodes early in the season are less likely to be accompanied by high grass pollen levels in northern Britain than in the south.

5.14 Geographical location will also influence the timing of peak pollen levels during the day (see paragraphs 5.20-5.25 below).

Figure 5.1 **A calendar of common aeroallergens in the United Kingdom. From Varney 1991,[4] reproduced by courtesy of Professor AB Kay.**



Daily exposure patterns

5.15 Day-to-day variations in pollutant concentrations largely reflect climatic conditions. Similarly, pollen levels tend to be high on days with high solar radiation, no precipitation, moderately high temperatures, and moderate windspeeds. With the exception of the windspeed, these are broadly the conditions which favour the development of high concentrations of O_3 in the atmosphere.

5.16 The daily patterns of pollen counts and pollutant concentrations during two grass pollen seasons are shown in Figures 5.2 and 5.3. Figure 5.2 shows data for central London (for 1992) based on data for the Paddington (grass pollen) and Bridge Place, London Bloomsbury and West London (pollution) sites. Figure 5.3 shows data for Harwell in 1993, a rural site at which the pollen and pollution monitors were co-located. The figures show time-series for NO_2 and for O_3 only, based on the maximum hourly mean concentration for each day. These were the pollutants for which significant correlations with grass pollen levels were found at both the urban and rural sites (Table 5.1). Clear evidence of an association between raised levels of grass pollen and pollutants is demonstrated. In contrast, no significant correlations were found with CO, NO, SO_2 and particles (PM_{10}) (urban site only).[6]

Table 5.1

Correlations between daily air pollution and grass pollen levels[6]

Pollutant	London (1992)	Harwell (1993)
Carbon monoxide	0.209	-
Nitric oxide	0.060	0.305
Sulphur dioxide	0.265	0.324
Nitrogen dioxide	0.511*	0.434*
Ozone	0.560*	0.585*
PM_{10}	0.369	-

* indicates correlation coefficients which are significant at $p < 0.05$

5.17 The time-series plots clearly show that there are days with high O_3 concentrations which are accompanied by high grass pollen levels, such as during the early June episode in 1993, or during the peak of ozone levels in mid-June in 1992. Conversely, there are periods, such as the episode of late June/early July 1993 when high O_3 concentrations are accompanied by relatively low grass pollen levels. These differences may reflect different meteorological conditions, or simply a seasonal change in pollen production. Thus, although there is overall a significant positive correlation, the association between high levels of pollen and high concentrations of O_3 is not consistent. In the case of NO_2 the pattern observed is similar, but the association is weaker than in the case of O_3.

5.18 In the case of fungal spores, the situation is more complex. In some species, spore release only occurs when free water is available to aid expulsion, and thus high spore levels are often associated with heavy rainfall or humid conditions. In contrast, in other species spore release tends to occur mainly in warm, dry conditions, when spores are most easily dislodged in turbulent wind movement. There does not appear to be a 'wash-out' effect of summertime rainfall on the levels of NO_2; in turbulent conditions there may be a slight rise in ground level O_3 due to better mixing.

5.19 While there are general patterns of relationships between climatic conditions and aeroallergen levels, it should be emphasised that any individual episode of high aeroallergen levels may have unique features. For example, the asthma/wheeze epidemic of June 24/25, 1994, which is described more fully below (see paragraphs 5.61-5.62), was associated with the passage of a severe thunderstorm over southern and eastern England. Pollen grains would be expected to be washed out of the atmosphere by heavy rainfall, although fungal spore release might follow the rain. An alternative hypothesis to explain the association of asthma episodes with thunderstorms, proposed by Knox,[7] is that pollen grains rupture under conditions of high humidity, leading to release of small allergen-containing starch granules into the atmosphere. In Melbourne, the level of these granules in the atmosphere was found to increase by a factor of 50 following heavy rainfall.[7]

Hourly exposure patterns

5.20 The timing of peak aeroallergen exposures during a day may also be significant in influencing patterns of simultaneous or sequential exposure with air pollutants.

5.21 Most grass species, including *Lolium perenne* (which releases the most common grass pollen in the UK) have regular daily patterns of anthesis, mostly in the morning. However, in other grass species, such as those of *Agrostis* and *Festuca*, release occurs mainly towards the middle of the day.[8] However, pollen release into the atmosphere from the flower may occur long after anthesis, and its dispersal is governed by windspeed and turbulence.

5.22 Peak grass pollen counts in London tend to occur in the late evening, with a mean at about 2000 hours; the lowest levels were found in the early morning, at about 0800 hours.[9] Work in the mid-1950s similarly gave a peak for grass pollen counts in London at 1900 GMT.[10] Thus, in terms of diurnal patterns, peak exposure is more likely to coincide with, or immediately follow, either a peak in O_3 concentration, or peaks of a vehicle-generated pollutant such as NO_2, which may be associated with the evening rush hour.

Figure 5.2 **Daily pollen counts (Paddington site) and maximum hourly mean concentrations of a) NO_2 and b) O_3 in central London (from Bridge Place, London Bloomsbury and West London sites) during the grass pollen season of 1992, 31 May to 21 July**

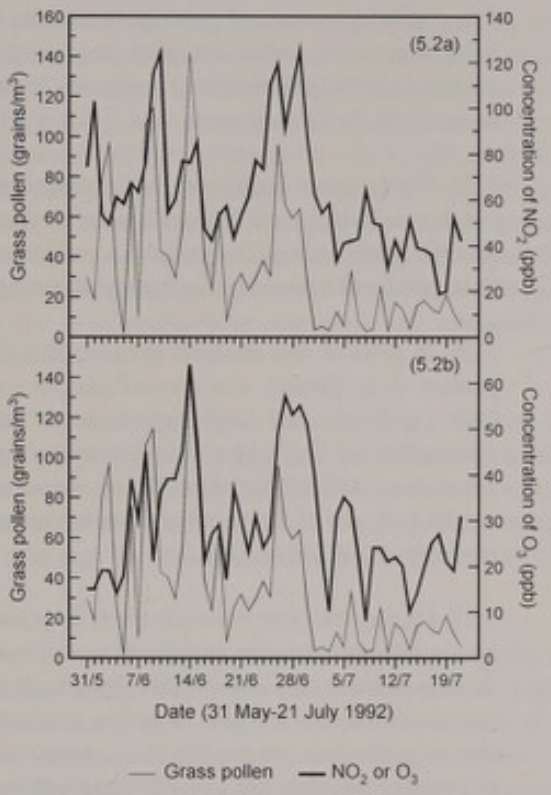
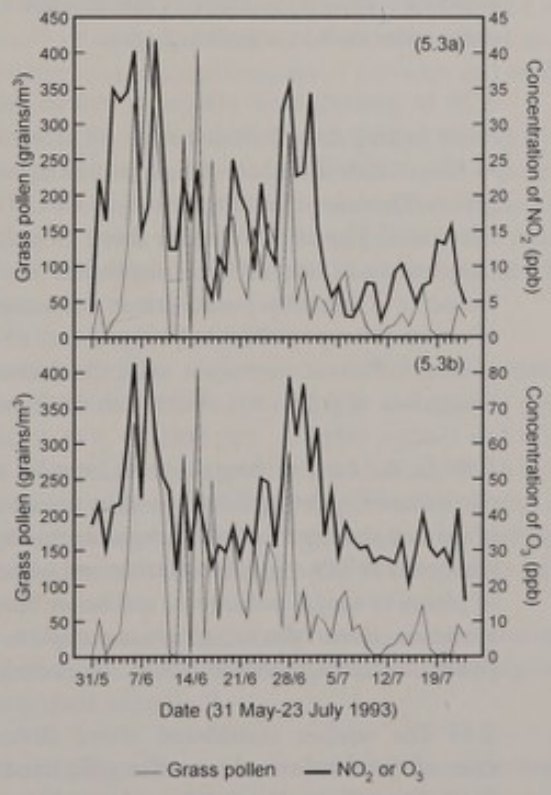


Figure 5.3 **Daily pollen counts and maximum hourly mean concentrations of a) NO_2 and b) O_3 at a rural site (Harwell), where pollen and pollution monitors are co-located, during the grass pollen season of 1993, 31 May to 23 July**



5.23 Peak levels of tree pollen tend to occur rather earlier in London than those of grass pollen,[9] with peaks for birch at about 1800 hours, and for plane at about 1600 hours; this is consistent with the shorter transport times for these pollens.

5.24 The timing of grass pollen peaks is often delayed in urban locations, as compared with the surrounding areas, because of the longer transport times from the source areas. Thus, although peaks of grass pollen occur in London in late evening, at Ascot, 35 km west of central London, the peak in grass pollen occurs in the late afternoon, at around 1600 hours.[11] Coincidence of peaks in O_3 concentration and grass pollen level may thus be more likely in rural areas.

5.25 While these comments indicate general trends in diurnal patterns, it should be emphasised that each day will have diurnal trends which in many cases, because of specific meteorological conditions, will not be consistent with this broad picture; for example, Steel reported occasional night-time peaks in grass pollen counts at the Ascot site.[11]

Summary

5.26 In general, this analysis suggests that for all four criteria – spatial pattern, seasonal pattern, daily pattern, and diurnal pattern – there is likely to be an association between high O_3 levels and high exposures to aeroallergens, especially grass pollen. This association is likely to be less pronounced for other pollutants, although there may be an association with peaks of pollutants associated with the evening rush-hour. However, a detailed picture of the patterns of co-occurrence will only be possible after more detailed analysis of actual UK data.

Reaction between air pollutants and aeroallergens

5.27 During the time it travels from its point of release to contact with a human subject, an aeroallergen may be modified by reaction with atmospheric pollutants. Furthermore, these pollutants may also modify the aeroallergen before its release to the atmosphere, and can also influence the rate of pollen production. Thus, before considering the evidence that air pollutants can modify the response of individuals to aeroallergens, there is a need to consider whether the aeroallergen itself can be modified by exposure to air pollutants.

Effects of air pollution on pollen production, size and viability

5.28 Air pollutants such as SO_2 and O_3 are known to reduce plant growth and development, and hence can reduce the production of pollen. There is evidence that, for some species, reproductive performance is more sensitive than vegetative performance; for example, Ernst and his colleagues showed that fumigation with 35 ppb of O_3 (70 $\mu g/m^3$) for four weeks completely prevented flower production by *Silene cucubalus* (bladder campion).[12] There is also evidence that conifer pollen grains in polluted areas are smaller than in unpolluted areas.[13]

5.29 In general, these effects on overall pollen production or on pollen characteristics relate to long-term pollutant exposure. However, there is evidence from both *in vitro* and *in vivo* studies that short-term exposure to air pollutants can have direct effects on pollen grains. These have been reviewed by Cox,[14] in an ecological context, and by Wolters and Martens.[15] The effects include those on pollen germination and pollen tube elongation. In some cases, the effect is dependent on other environmental factors. For example, Bosac *et al.* recently found that *in vitro* exposure to 200 ppb SO_2 (572 $\mu g/m^3$) had no effect on dry rape pollen, but a significant effect on germination and tube length on moist pollen.[16] This is consistent with the proven sensitivity of the germination and tube elongation of pollen to contact with solutions of high acidity.[14]

Effects of air pollutants on production of other aeroallergens

5.30 In the case of fungal spores, similar arguments apply. Certain pollutants, and in particular SO_2, are well known to be toxic to plant pathogens, and the historical absence of certain plant pathogens, such as blackspot of roses, in urban areas of the UK has been attributed to SO_2. Sulphur dioxide and other pollutants may also alter the susceptibility of plants to fungal pathogens, and hence alter the prevalence of fungal spores indirectly. However, these effects are often complex, with both positive and negative effects of pollutants having been described, depending on the nature of the fungal pathogen.[17]

Direct effects of air pollutants on aeroallergens

5.31 The studies considered above demonstrate that air pollutants can alter the rate of production of aeroallergens, and also cause gross changes, for example in pollen size and viability. It is also possible that air pollutants could react

chemically with allergen molecules bound into the wall of the pollen grain or fungal spore.

5.32 Pollutants such as O_3 and SO_2, which are known to react chemically both with individual amino acids, and with proteins, may cause changes in the allergenicity of aeroallergens. The potential for such effects has been demonstrated by Ruffin *et al.*,[18] who exposed pollen of oak, fescue and elm to SO_2, NO_2 and CO, individually or in combination. They were able to demonstrate in most cases an increase in free amino acid content, which they suggested was of significance because those species having pollen with a high allergenic potential tend to have a high free amino acid content. There was also some evidence of effects on low molecular weight proteins. In a study with cell wall extracts of red oak pollen,[19] pollutant exposure was shown to affect both levels of histamine release in human leucocyte suspensions and the patterns of antibody formation after injection into rabbits, thus demonstrating the potential for pollutant-induced changes in pollen allergenicity. However, the pollutant exposures used in these studies (10,000 ppm for 3 minutes) bear absolutely no relationship to real environmental exposures in the UK.

5.33 It should be noted that there is increasing evidence that allergenic activity is associated with micronic and submicronic particles, which might be pollen fragments, starch granules or other plant material.[7,20,21] Whatever the source, these smaller particles may be of considerable significance because they can penetrate deeper into the lung. Furthermore, they may be physically associated with pollutant particles, or react with air pollutants.

Summary

5.34 It is clear that there are many potentially significant interactions between aeroallergens and pollutants when they co-occur in high concentrations in the atmosphere which could have implications for the impact of air pollution episodes on allergic disease. However, there is very little direct evidence, due to the lack of studies, to demonstrate that such effects actually occur at the pollutant concentrations found in UK episodes, or that they have significant health implications.

Combined effects of air pollutants and aeroallergens

Animal studies

5.35 Concern about the spatial and temporal association between the prevalence of allergic rhinitis and the numbers of motor vehicles in Japan[22] has led to a number of studies with diesel exhaust particles. These Japanese studies, with mice, have demonstrated that diesel particles can act as an adjuvant and increase production of IgE. This has been demonstrated by intraperitoneal injection of a mixture of diesel particles and ovalbumin,[23] or of a combination of diesel particles and cedar pollen,[23] and by intranasal administration of combinations of particles and ovalbumin[24,25]

5.36 In the case of O_3, a number of studies have provided evidence of an enhanced antibody response to antigen challenge. Osebold *et al.* exposed mice to 500 ppb or 800 ppb O_3 (1000 or 1600 $\mu g/m^3$), followed by nebulized ovalbumin, and found an enhanced immune response in terms of systemic anaphylaxis.[26] A similar response was produced by prior exposure to sulphuric acid aerosol (1 mg/m^3); in addition, there was evidence of synergistic interaction between the pollutants.

5.37 Matsumura had earlier shown similar effects in guinea pigs at much higher O_3 concentrations (5000 and 8000 ppb, 10,000 and 16,000 $\mu g/m^3$), as well as at high concentrations of NO_2 (70,000 ppb, 132,000 $\mu g/m^3$) and SO_2 (330,000 ppb, 940,000 $\mu g/m^3$).[27] The effect of O_3 was attributed, at least in part, to increased antigen absorption and retention in the guinea pig lung.[28] Gershwin *et al.* also found a four-fold greater increase in IgE-containing cells following inhalation of ovalbumin in mice when this was preceded by exposure to 500 or 800 ppb O_3 (1000 or 1600 $\mu g/m^3$).[29]

5.38 Effects of O_3 in increasing the response to antigen challenge were also reported in dogs by Yanai *et al.*, at a concentration of 3000 ppb (6000 $\mu g/m^3$); this response was only observed in sensitised animals.[30]

5.39 In the case of SO_2, exposure to a relatively low concentration (100 ppb, 286 $\mu g/m^3$, for 8 hours on 5 consecutive days) facilitated allergic sensitisation to ovalbumin

(assessed as bronchial obstruction following a subsequent ovalbumin challenge) in 4/6 guinea pigs, with increased antibody concentrations being found in bronchoalveolar lavage.[31]

5.40 By contrast, studies, in dogs, of short term (5 minute) exposures to ozone (1 ppm, 2 mg/m^3) have demonstrated an attenuation of the response (resistance to flow through the collateral system) to allergen administered up to 24 hours later.[32,33] Also, exposure of rabbits, which had been sensitised at birth to house dust mite allergen, for 2 hours/day to NO_2 (4000 ppb, 7520 µg/m^3) from birth to 3 months of age had no effect on the response to histamine or methacholine.[34]

5.41 In summary, animal studies provide only rather limited evidence of pollutant/aeroallergen interactions; also, many of these studies have used very high pollutant concentrations. While this evidence does offer some support for the hypothesis that air pollutants can increase animal sensitivity to antigen challenge, its relevance to the actual effects of UK episodes is very limited.

Controlled human studies

5.42 Molfino *et al.* reported a study in which the effect of exposure for 1 hour to 120 ppb O_3 (240 µg/m^3) on subsequent responses to an inhaled allergen was examined.[35] The study involved seven atopic asthmatic subjects with positive skin prick tests to either ragweed or grass allergen. Subjects were challenged with allergen, the dose being increased until a 15% decrease in FEV_1 or a 40% decrease in vital capacity was recorded. On test days subjects were exposed to either air and allergen diluent (placebo), air and allergen, O_3 and allergen diluent or the combination of O_3 and allergen. Exposure to the O_3/allergen combination always followed the other exposures. Methacholine challenge between exposures demonstrated no carryover of effects from one exposure to the next.

5.43 Ozone alone had no effect on airway function, but significantly reduced, by about 50%, the concentrations of allergen needed to produce the indicative changes in airway function. There was, however, variability in the response between individuals, with one subject apparently showing reduced responsiveness to allergen challenge after exposure to O_3.

5.44 There are a number of limitations in the design of this study. In particular, the design was changed during the study, the study was single blind, only seven subjects took part, and there was only one week recovery time allowed between the different treatments. Nevertheless, this was the first reported study of interactions between O_3 and allergen exposure, and is important in suggesting that short-term exposure to concentrations of O_3, at levels which do occasionally occur in the UK, can increase the responsiveness of atopic asthmatics to allergen exposure.

5.45 A more detailed study of the effects of O_3 on bronchial responses to inhaled allergens has been undertaken by Jörres *et al.*, using a higher exposure of 250 ppb O_3 (500 µg/m^3) for 3 hours.[36] Three groups of subjects were recruited: 24 subjects who were atopic asthmatics, 12 subjects with allergic rhinitis but no asthma symptoms, and 10 control subjects. Subjects were exposed to O_3 or filtered air through a mouthpiece during intermittent exercise. On the first day the subjects received a methacholine inhalation challenge. On the second day, the subjects were exposed to O_3, and their airway response to methacholine was determined 1 hour later; while on the third day an allergen inhalation challenge alone was given. On the fourth and fifth days, the subjects received either filtered air or O_3 in randomised order with subjects being blind to the treatment; these were preceded and followed by methacholine challenge, and then by allergen challenge. There was a period of 4 weeks or more between the third, fourth and fifth study days.

5.46 The O_3 treatment alone caused a significant decrease in FEV_1, of between 10 and 16%, in all three subject groups. For subjects with asthma, the allergen concentration required to produce a 20% decrease in FEV_1 ($PD_{20}FEV_1$) was determined, and found to be significantly reduced, by 1.74 doubling doses, by prior O_3 exposure. In only one of the 24 subjects was O_3 found to increase the $PD_{20}FEV_1$. The mean decrease in FEV_1

caused by the highest allergen challenge was significantly increased by O_3, from 10% to 28%. In subjects with allergic rhinitis, only the reduction in FEV_1 was evaluated; this also increased significantly, from 1% to 8%. No significant effects of allergen challenge were found in the healthy subjects. Ozone was also found to significantly decrease the $PC_{20}FEV_1$ value for methacholine in the asthmatic subjects, but not in those with rhinitis. No significant correlations were found between the responses of subjects in terms of the O_3-induced changes in responsiveness either to allergen or to methacholine, or the O_3-induced changes in lung function.

5.47 This study[36] had an improved study design compared with that of Molfino *et al.*,[35] with the O_3 and control treatments randomised, a longer time period between treatments, and an increased number of subjects. It is also possible to compare the effects of allergen challenge following O_3 not only with those following filtered air, but also with those on the third day, when only an allergen challenge was performed: the results were generally consistent. The lack of a correlation between O_3-induced changes in lung function and allergen responsiveness is consistent with the assumption that the latter is more closely linked to inflammatory changes induced by O_3 and also with recent suggestions that these are not associated with lung function changes.

5.48 This study provides strong support for the assertion that O_3 exposure can increase allergen responsiveness. However, the O_3 concentration used was high, and has only ever been recorded in the UK in the exceptional summer of 1976. More studies are needed at realistic O_3 concentrations.

5.49 The effect of O_3 on response to allergen has also been examined with nasal antigen challenge. Twelve subjects with a history of seasonal allergic rhinitis were exposed while at rest to 500 ppb O_3 (1000 $\mu g/m^3$) or filtered air for 4 hours. This was followed by nasal challenge with varying levels of either grass or ragweed antigen.[37] There were no significant effects of O_3 pre-exposure on the severity of self-recorded symptoms of rhinorrhoea, sneeze or chest tightness in response to antigen challenge. However, this concentration of O_3 was sufficient, in the absence of antigen challenge, to increase the severity of lower respiratory tract symptoms, and to cause an inflammatory response in the nose, with an increased numbers of eosinophils and neutrophils recovered in nasal lavage. Since the O_3 concentrations in this study were well above those recorded in the UK, and are clearly sufficient to have a significant impact on the nose without antigen challenge, their relevance to the hypothesis that O_3 may alter susceptibility to nasal challenge with aeroallergens at ambient UK levels is limited. This type of study needs to be repeated at lower concentrations of ozone.

5.50 A recent study[38] used a 'split nose' design to investigate the effects of O_3 exposure on subsequent inflammatory responses to allergen exposure, by applying allergen to one nostril, and saline to the other. The authors suggest that nasal responses to O_3 can be used as a surrogate for its effects on bronchial mucosal inflammation in asthmatic subjects. The study involved exposure of 10 allergic asthmatic subjects, who were sensitive to house dust mite, to clean air or 400 ppb O_3 (800 $\mu g/m^3$) for 2 hours while at rest; exposures were separated by at least 4 weeks. Nasal lavage was performed before exposure, immediately after exposure, and then after subsequent nasal allergen/saline challenge. Allergen doses were increased in ten-fold steps until a standard level of symptom severity was reached; in 5 of the 10 subjects this required 1/10 of the dose after pre-exposure to O_3 rather than clean air. There was evidence that O_3 pre-exposure increased the influx of eosinophils and neutrophils resulting from allergen challenge, even though the allergen dose used was lower in half the subjects. Data from the control nostril indicated that O_3 alone also had inflammatory effects, with increased eosinophil and neutrophil influx being detected.

5.51 The effect of prior exposure to NO_2 on response to nasal allergen challenge has recently been reported.[39] Exposure to allergen after either air or NO_2 (400 ppb, 752 $\mu g/m^3$; for 6 hours) significantly increased mast cell tryptase in nasal lavage fluid from patients with a history of seasonal allergic rhinitis. However, a significant increase in eosinophil cationic protein in response to allergen was only observed when the prior

exposure was to NO_2 (exposure to NO_2 without allergen had no effect on eosinophil cationic protein levels in the nasal lavage). This suggests that NO_2 increases eosinophil activation in the early phase response to allergen provocation in allergic rhinitics.

5.52 The effects of very short-term exposures (5 mins) to NO_X and SO_2 were tested on mite-sensitive asthmatic children by Huang *et al.*[40] The concentrations used were 70-120 ppb (200-343 $\mu g/m^3$) for SO_2 and 450-500 ppb for NO_X (concentrations of nitric oxide and NO_2 unspecified), but no significant effects on bronchial sensitivity to either methacholine or allergen challenge was found after these short exposure times.

5.53 Two recent UK studies have investigated the effect of prior exposure to air pollutants on airway responses to bronchial challenge with house dust mite in subjects with mild asthma. The study by Devalia *et al.*[41] investigated the interaction between two pollutants (SO_2 and NO_2) and an allergen. Eight subjects were exposed in a controlled environment chamber for 6 hours to room air, 400 ppb (752 $\mu g/m^3$) NO_2 alone, 200 ppb (572 $\mu g/m^3$) SO_2 alone, and 400 ppb NO_2 plus 200 ppb SO_2. After each treatment the response of the subjects' FEV_1 to allergen inhalation was determined. The four pollutant treatments were given on four separate occasions, each at least a week apart, with the order being randomised among the subjects and the subjects being unaware of the order.

5.54 No significant effects of any of the pollutant treatments alone was found on FEV_1 or FVC. The inhaled allergen dose estimated to produce a 20% fall in FEV_1 ($PD_{20}FEV_1$) was significantly reduced, by approximately 60%, by the NO_2 plus SO_2 treatment compared with the control treatment. The $PD_{20}FEV_1$ values were also reduced by 41% by NO_2 alone, and by 32% by SO_2 alone, but these effects were not statistically significant at $p = 0.05$.

5.55 The second study[42] only investigated the effects of NO_2, but used two concentrations (100 ppb and 400 ppb, 188 and 752 $\mu g/m^3$) and studied both the early and late asthmatic responses. Eight subjects were exposed to NO_2, or to room air, for 1 hour through a mouthpiece; each exposure was at least one week apart, with the order being random and neither subjects nor investigators being aware of the order. The inhaled allergen dose previously estimated to produce a 15% fall in FEV_1 was administered immediately after gas exposure, and FEV_1 was then measured at 20-minute intervals in the first hour, and at hourly intervals during the next six hours.

5.56 Both the early and late responses, expressed as the maximum percentage change in FEV_1 during the relevant period, were significantly increased by prior exposure to 400 ppb NO_2 (752 $\mu g/m^3$). However, the mean size of the effects was relatively small: from -14.6% in air to -18.6% in NO_2 in the case of the early response, and from -2.8% in air to -8.1% in NO_2 for the late response. At exposure concentrations of 100 ppb NO_2 (188 $\mu g/m^3$) there was no significant effect on either the early or late responses.

5.57 The different designs of these two studies makes any direct comparison of their findings difficult. It is also important to note that the simultaneous combination[41] of 400 ppb NO_2 and 200 ppb SO_2 is unlikely to occur in any UK episode, while Tunnicliffe *et al.* specifically refer to 400 ppb NO_2 as a concentration which is much more likely to occur in the indoor environment than in the UK outdoor environment.[42] Nevertheless, the studies both provide further direct evidence that prior exposure to air pollutants can potentiate responses to allergens.

5.58 A recent study[43] has extended the observations of the effects of diesel exhaust particles (DEP) on IgE to human subjects. Eleven subjects were subjected to 0, 0.15, 0.3, or 1.0 mg of DEP in 200 µl of saline nasal spray, and nasal washes were performed 0, 4, 7 and 10 days after the nasal provocation. The levels of IgE in the nasal lavage were increased in all 11 subjects 4 days after the 0.3 mg treatment, but no significant effect of the higher or the lower DEP exposures was found. The effect on IgE levels was lost after 7 and 10 days. The levels of IgG, IgA and IgM were not affected by DEP exposure, but the number of IgE-secreting cells was increased by an order of magnitude 4 days after exposure to 0.3 mg DEP. These results are consistent with the findings with mice, in

which DEP increased the IgE, but not the IgG, response to ovalbumin. The dose of DEP found to induce the IgE response was stated to be equivalent to that produced by breathing outdoor air in Los Angeles for 24 hours, and the authors suggest that the response may be associated with the polycyclic aromatic hydrocarbon content of DEP. These results indicate the possibility that exposure to DEP could increase the likelihood of developing respiratory allergic disease, and further studies are clearly needed with this pollutant.

5.59 In summary, there is now a body of information which suggests that prior exposure to a number of air pollutants can increase the response of human subjects to allergen challenge. Further work is underway and will be reported in the next two years. The work reported to date has used relatively high concentrations of pollutants, and further examination of the hypothesis is needed at lower pollutant concentrations.

Epidemiological studies

5.60 Outbreaks of large numbers of cases of severe asthma attacks have been reported on many occasions in the literature.[44-46] These are often associated with specific meteorological conditions, such as severe thunderstorms. A major recent example in England was the outbreak associated with thunderstorms in June 1994.

5.61 On the night of June 24/25, 1994 the Accident and Emergency (A&E) departments of many London hospitals were overloaded with large numbers of cases presenting with asthma/wheeze. Hospitals outside the London area were also affected.[46] Subsequently, the Chief Medical Officer sought information from Directors of Public Health in England in order to define the scope and extent of this epidemic. Returns made to the Department of Health suggested that four of the eight Regional Health Authorities had been particularly affected; these were Anglia and Oxford, North Thames, South Thames, and Trent (Figure 5.4). The majority of patients were adult and many had not been known to be asthmatic previously. It was clear that many of the patients who presented at A&E departments attended within a very short time span (Figure 5.5). The timing and geographical distribution of cases suggested that there was an association with a thunderstorm that passed over London during the evening of June 24.[46-48]

5.62 Linkage of asthma epidemics to thunderstorms occurring at Birmingham, England[49] and Melbourne, Australia[50] during the 1980s has been reported previously. In these episodes the levels of fungal spores[51,52] or grass pollen/pollen fragments[7,50] had been raised at the time of the epidemic. The peak of the 1994 grass pollen season was reached in the period June 20-24. Many areas in the southeast experienced the highest daily average grass pollen counts of the year on June 23. For example, in London the daily average grass pollen count reached 258 grains/m^3. This was the highest daily count recorded at the monitoring site since 1987. In the Midlands, most areas recorded peak counts on June 21/22 and, although grass pollen counts remained high, a decrease on June 23/24. Other pollen types recorded during this period included *Tilia* (lime), *Plantago* (plantain), *Rumex* (dock), *Castanea* (chestnut) and *Sambucus* (elder), but these were in relatively low concentrations (the 1994 pollen data were kindly supplied by Dr Jean Emberlin). At this time there was a massive rise in counts of fungal ascospores of *Phaeospheria nigrans* and Diatrypaceae.[47] The low proportion of children in the A&E cases is suggestive of a causal association with fungal spores, as sensitisation to fungal spores occurs later in childhood than sensitisation to pollen. Concentrations of air pollutants in the London area during that week had been highest on June 24, probably because of the calm, still conditions that preceded the storm. In the London area the highest hourly average concentrations of O_3, NO_2 and SO_2 were 44, 126 and 48 ppb (88, 237 and 137 µg/m^3) respectively, none of these values exceed the WHO air quality 1-hour guidelines; the highest hourly average concentration of PM_{10} in the London area was 102 µg/m^3. In southern rural areas the maximum hourly O_3 concentration was, as would be expected, higher: 84 ppb (168 µg/m^3; at Sibton). The levels were not unusually high and would not have been expected to cause serious health effects. Research groups are investigating the hypothesis that the epidemic was associated with raised levels of aeroallergens.

5.63 In Barcelona, 26 asthma epidemics occurred between 1981 and 1987, affecting in

Figure 5.4 **Attendance on the night of June 24/25, 1994 at hospital A&E departments in England with asthma/wheeze. The data are grouped by Regional Health Authority and represent: a) the ratio of attendances on that night to equivalent attendances on the night of July 1/2, 1994, (the ratios are based only on those hospitals which returned quantitative data for both nights); and b) total numbers of persons attending on the night of June 24/25, 1994.**

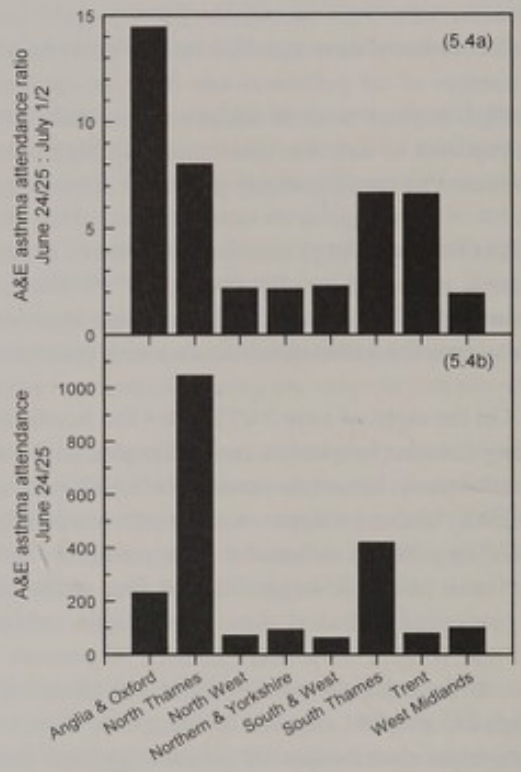
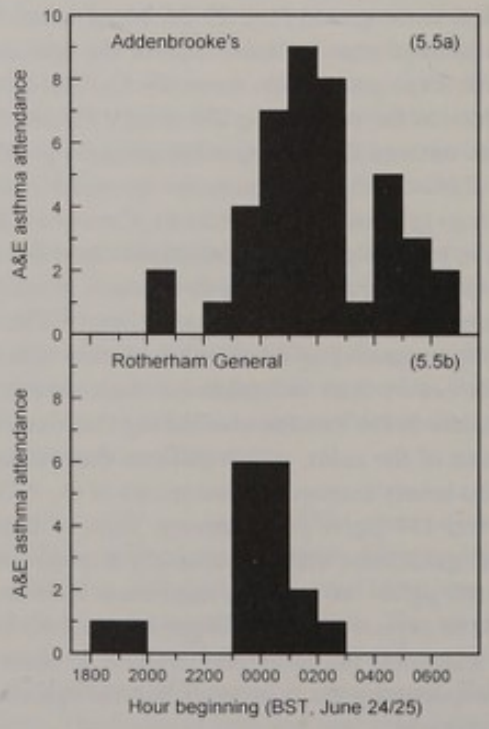


Figure 5.5 **Time course of attendance with asthma/wheeze on the night of June 24/25, 1994 at the A&E departments of: a) Addenbrooke's, Cambridge (Anglia and Oxford RHA); and b) Rotherham General, South Yorkshire (Trent RHA).**



total about 1000 patients, and causing 24 deaths. Although air pollution was initially considered as a possible cause, epidemiological investigation clearly demonstrated that inhalation of soybean dust from the unloading of soybean cargoes was the primary cause.[45] This was confirmed, as the asthma outbreaks ceased once the dust emissions were properly controlled.[53,54] Asthma epidemics also occurred in New Orleans during the 1950s and 1960s, though the causes were not fully understood at the time.[44,55] Recent examination of historical data, published in abstract,[56] indicates that asthma epidemics were 2.5 times more likely to have occurred on days when a ship carrying soy was in the harbour.

5.64 However, there has been some recent analysis of the hypothesis that, in Barcelona, the presence of air pollutants increased the likelihood of an asthma outbreak on a given day when soybeans were being unloaded.[57] This suggests that there was such an increase both when meteorological conditions were appropriate and when pollutant concentrations, particularly those of smoke and SO_2, were increased. However, this could be interpreted as indicating that the meteorological conditions which favoured the development of high atmospheric soybean particle concentrations also favoured the development of high pollutant concentrations.

5.65 In general, most analyses of the effects of air pollution episodes on the severity of the symptoms of allergic disease have considered only air pollution levels, and not those of aeroallergens. Similarly, panel studies of asthmatics have generally only considered air pollution or aeroallergen levels separately, and not investigated in any formal statistical manner the possible interactions of these two factors. Furthermore, most studies of asthmatics have not distinguished atopic individuals, and therefore are difficult to interpret in terms of the rôle of pollutants and aeroallergens in combination. Where aeroallergen data have been examined, they have only been related directly to the measured health outcome, without consideration of the levels of air pollutants.

5.66 In a recent series of studies of hayfever in London, a diary approach has been used to evaluate whether the symptoms recorded by a recruited panel of subjects sensitive to grass pollen were exacerbated by air pollution.[6] The daily symptom severity was firstly related to the daily levels of pollen measured in London over the season of 1992. Symptoms showed a linear relationship with a modified pollen count, which incorporated a delayed response to pollen exposure on previous days. Each day was then assigned to a high or low category for each individual pollutant, based on the maximum hourly concentrations on each day, and analysis of covariance was used to assess whether the relationship between the modified pollen count and the mean symptom severity differed significantly between the two levels of pollution. No significant effects were found for SO_2, NO_2, CO or black smoke, but significantly higher levels of symptom severity were found for some symptoms on days with higher O_3 concentrations.

5.67 A similar study was conducted in rural Oxfordshire in 1993. Here, pollen levels are markedly higher than in London, and there was evidence of a saturation of symptom severity above pollen levels of 250 grains/m^3. However, on days with lower pollen levels, symptom severity was again higher on days with higher O_3 levels, an observation which is consistent with the results of the London studies.[6]

5.68 While these studies do not necessarily indicate a causal relationship with O_3, they suggest a need for further controlled studies of co-exposure of sensitive subjects to O_3 and grass pollen at a range of exposure levels.

Summary and conclusions

5.69 There is emerging evidence from controlled human exposure studies and epidemiological studies that exposure to air pollutants such as O_3, NO_2 and diesel exhaust particles can increase the response of subjects to subsequent allergen challenge. Furthermore, there appears to be some consistent mechanistic explanation for these responses, associated with the inflammatory effects of the pollutants. At present, the number of published studies is very small (no more than 2 or 3 for each pollutant); in addition the number of subjects in many of the studies is very small, and further work is needed for these, and other, pollutants to provide a sounder basis for this conclusion.

5.70 It should be emphasised that the fact that pollutants *can* produce such responses does not demonstrate that there will be synergistic effects of exposure to air pollutants and aeroallergens in typical UK episodes. This would require:

- a considerable body of additional information from controlled human studies about the interactions between allergen challenge and exposure to the pollutant concentrations typical of UK episodes;

- more detailed analysis of the patterns of co-occurrence of air pollutants and aeroallergens. The preliminary, and largely qualitative, analysis carried out in this chapter indicates the likelihood of spatial and temporal associations between high grass pollen levels and high O_3 concentrations. However, more rigorous quantitative analysis is needed both for O_3 and for other pollutants. This analysis should not neglect the importance of allergenic micronic or submicronic fragments as well as whole pollen grains;

- epidemiological studies specifically designed to investigate the interactive effects of air pollutants and aeroallergens on populations in the UK;

- further studies to elucidate the mechanisms which underly these interactions. These studies should encompass not only the immunological responses of human subjects, but also the chemical and physical interactions between allergens and pollutants in the atmosphere. The latter have been little studied.

5.71 Despite these uncertainties there is some evidence of an increased sensitivity to allergens at the high concentrations which characterise episodes currently classified as "**Poor**" or "**Very Poor**" air quality. During these episodes, it would sensible to recommend that sensitive individuals should take measures to reduce their exposure to aeroallergens, especially as such measures are often consistent with measures which would also reduce their pollutant exposure.

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Annex 5A

Physiological and Immunological Responses to Inhaled Allergens

Physiological responses to inhaled allergens

5A.1 In subjects specifically sensitised to inhalant allergens, challenge of the upper or lower airways with that allergen will reproduce the features of rhinitis and asthma, respectively. With high concentrations of soluble allergen, there occur both "early" and "late" responses which result from the release of bioactive mediators of inflammation.[1]

5A.2 The early reaction is IgE dependent and follows from activation of mast cells in the mucosa with non-cytotoxic release of both preformed (histamine, heparin, tryptase) and newly-generated (prostaglandin D_2, PGD_2; leukotriene C_4, LTC_4; platelet activating factor, PAF; reactive oxygen) mediators.[2] In the nasal mucosa these mediators produce rhinorrhoea, sneezing, nasal blockage and the engorgement of veins in the mucosa.

5A.3 The conjunctiva is part of the integument and, as such, normally contains mast cells of the connective tissue type (*i.e.* containing chymase and other proteases in addition to tryptase), in contrast to the nasal and bronchial mucosa in which the tryptase-only mast cell dominates. However, in allergic conjunctivitis there is an influx of "mucosal"-type mast cells into the conjunctivae and it is these cells that respond to aeroallergen.[3] The characteristic symptoms are soreness and itching, excess lacrimation, redness and conjunctival oedema that, in severe cases, can involve both the bulbar and tarsal conjunctivae.

5A.4 In the lower airway an inhalation challenge with allergen produces bronchoconstriction of rapid onset reaching a maximum 10-15 minutes after exposure and lasting for up to two hours. Airway narrowing occurs predominantly as a result of contraction of airway smooth muscle induced by LTC_4 (and its metabolite LTD_4), PGD_2 and histamine in descending order of potency (1000:100:1). Since these mediators are also vasoactive, increased microvascular permeability and mucosal swelling may make a minor contribution to the airflow obstruction, particularly in the more peripheral airways.[2] Because children have smaller airways, this aspect of the inflammatory response may be particularly important in childhood wheezing associated with allergen exposure. Two further factors influence the overall magnitude of the early response:

- stimulation of non-myelinated afferent neurones by mast cell mediators to produce central (muscarinic) and local (neuropeptide) reflex augmentation of smooth muscle contraction and microvascular permeability;

- the release of secondary mediators, a process that includes the activation of kallikreins to generate kinins such as bradykinin and lysbradykinin which, in themselves, have potent mediator activities.

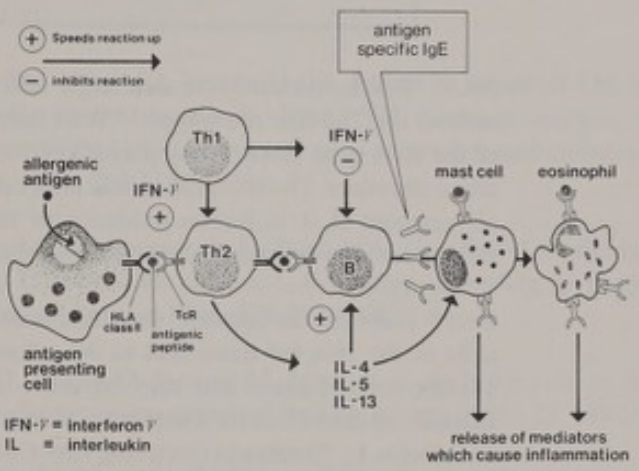
Immunological responses to inhaled allergens

5A.5 Allergic manifestations occurring on exposure to aeroallergens are observed in those with a genetic predisposition towards developing an IgE response, *i.e.* in atopic individuals. Approximately 40% of the population are atopic and, worldwide, the prevalence seems to be increasing.[4] A number of genetic markers of atopy have been identified and include both allergen-specific (human lymphocyte antigen, T-cell receptor)[5,6] and non-specific (polymorphisms of the ß-chain of the high affinity IgE receptor on mast cells, basophils and dendritic cells[7] and linkage to chromosome 5q where the interleukin-4, IL-4, gene cluster is located).[8]

5A.6 Sensitisation follows from the production of IgE directed towards specific peptide sequences (epitopes) on allergen protein. The sequence of events which lead to the isotype switching of B-cells from IgM to IgE synthesis is depicted in Figure 5A.1. Allergens are first recognised by dendritic cells: the antigen-presenting cells found in the epithelium and submucosa. Once internalised by these cells, antigens are broken into

component fragments and a single fragment is presented back on the surface of the cell in the cleft of the heterodimeric HLA class two molecules. Migration of the dendritic cell to local lymphoid tissue initiates the second stage, namely the presentation of the allergen fragment to the helper ($CD4^+$) T-cell receptor. In those predisposed towards atopy, receipt of this signal by T-cells (involving a number of other cell surface accessory molecules) results in T-cell proliferation and differentiation to form a clone of allergen-specific T-cells. These, in the presence of a small amount of IL-4, express cytokine genes encoded in the IL-4 cluster (including the genes encoding for IL-4, IL-13, IL-5, IL-3, GM-CSF and IL-9). Because of this cytokine repertoire these cells are designated Th2-like to differentiate them from Th1-like cells which elaborate a separate array of cytokines (IFN-γ, TNF-ß, IL-8, IL-2) involved in the delayed (Type IV) hypersensitivity reaction.[9,10] In the absence of T-B cell contact, but in the presence of IL-4 alone, B-cells can generate IgE non-specifically and might account for the high circulating levels of IgE for which no allergen specificity can be found.[10] The process of primary sensitisation probably starts in early life (and possibly *in utero*).[11] Most individuals who develop common aeroallergen sensitisation do so by the age of 11 years and more than 80% will have done so by the age of 7 years.

Figure 5A.1 **Schematic representation of the cellular and cytokine components of the IgE-dependent allergic tissue response**

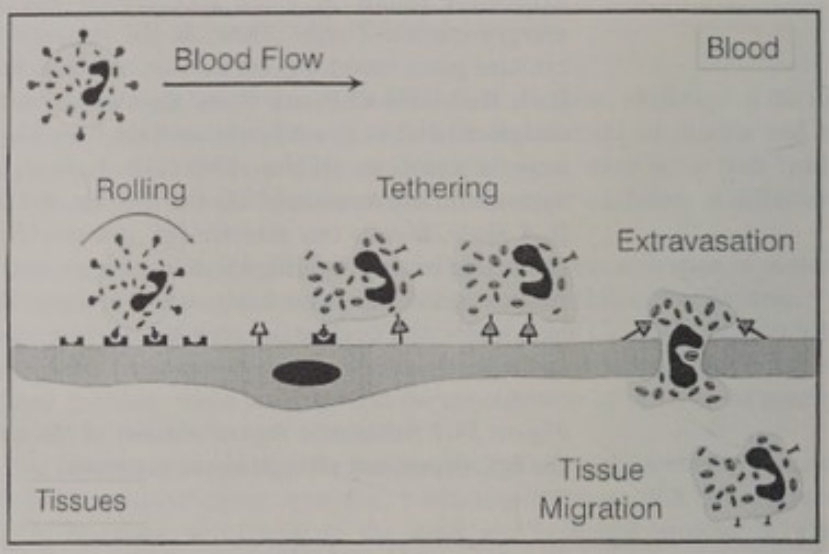


5A.7 Sensitisation of a tissue occurs when systemic or local IgE binds to IgE receptors on mast cells and basophils (FcεRI) and eosinophils, monocytes/macrophages and platelets (FcεRII). Sensitisation may be augmented with further allergen exposure and obeys the same kinetics as the secondary response involving other immunoglobulins. Augmentation of the primary and secondary IgE response can be achieved by certain adjuvants. For example, cigarette smoking in pregnancy increases subsequent IgE production in the infant,[12] while in an occupational setting occupational asthma involving IgE mechanisms occurs more frequently and is more severe in smokers.[13] There are animal experiments that suggest a similar effect may occur with high concentrations of other air pollutants such as SO_2 and O_3,[14,15] but whether this occurs at ambient pollutant levels is not known.

5A.8 Activation of sensitised mast cells with allergen not only releases mediators involved in the early response, but also generates cytokines (TNF-α, IL-4, IL-5, IL-6, IL-8) that are involved in the recruitment and activation of eosinophils and mononuclear cells. Interaction of TNF-α and IL-4 with the microvascular endothelin upregulates specific cell adhesion molecules (CAMs) that, by interacting with specific ligands on passing leucocytes, result in the entrapment and subsequent recruitment of the cells into the perivascular space (see Figure 5A.2). Vascular expression of P-Selectin, E-Selectin, ICAM-1 and VCAM-1 are upregulated in turn resulting in the neutrophil, eosinophil, mononuclear cells sequence of the late reaction.[16] Interaction of leucocytes with CAMs and further interactions with tissue chemoattractants prime the cells for subsequent mediator secretion. Cytokines generated in the tissue serve to prolong inflammatory cell

survival: *e.g.* IL-5 and GM-CSF for eosinophils, stem cell factor for mast cells, and IL-4 for Th2 lymphocytes.

Figure 5A.2 **Schematic representation of leucocyte (eosinophil)-endothelial interactions in the pathogenesis of the allergic inflammatory response**



5A.9 T-cells recruited into an allergic inflammatory response are dominated by $CD4^+$ cells of the Th2-like phenotype.[17] With their capacity to generate and secrete cytokines of the IL-4 gene cluster, they play a key rôle in the more chronic phase of asthma and allied disorders. The recognition that mast cells, basophils and Th2-like lymphocytes can all generate IL-4 is further evidence of the complex interplay between the various inflammatory components of the allergen-induced tissue response.

5A.10 Outwith the immune system, cytokines and other mediators from constitutive cells of the affected tissue add to the inflammatory signals that augment and prolong allergic inflammation and may be more important than hitherto recognised. These include epithelial cells (secreting IL-6, IL-8, RANTES, nitric oxide (NO) and endothelin-1), fibroblasts (secreting GM-CSF, IL-8 and stem cell factor) and endothelial cells (secreting IL-8, GM-CSF, endothelin and NO).

5A.11 A knowledge of these mechanisms has provided a rational understanding of how various therapeutic agents work in allergic disease: hyposensitisation by down-regulating T-cell function, corticosteroids through inhibitor T-cell and other cytokine production and sodium cromoglygate and nedocromil sodium through inhibition of mast cells and neuropeptide-containing neurones.

5A.12 In the upper air passages, but especially in the lower airways, the early response is followed after about 2-4 hours by a late response characterised by an influx of neutrophils followed by eosinophils and, finally, activated mononuclear cells.[16] Through the release of autacoids (LTC_4, PAF) and reactive oxygen, these cells produce a more prolonged influence on airway function with a prominent effect on the microvascular bed and, in the lower airways, contraction of smooth muscle. In the lower airways (and on occasions in the nose) the late reaction is accompanied by a progressive increase in airway responsiveness to a range of constrictor stimuli and, while the late reaction may last for up to 24 hours, enhanced airway responsiveness may persist for up to three weeks.[1] Overall, the late reaction and the attendant airway hyperresponsiveness is thought to reflect more closely the events that occur through the pollen season. However, it is relatively uncommon that sensitised individuals experience massive allergen challenges; it is more likely that they are subject to a constant or steadily changing allergen load during the pollen or fungal seasons.

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Chapter 6

Controlled Chamber Studies with Air Pollutant Mixtures

Assessment of interactions

6.1 Methods to assess interactions between drugs are well developed in clinical pharmacology and the same principles are relevant to studies of the interactions between air pollutants. An interaction between two substances is described as:

- *Antagonistic* – when the response is less than the sum of the response to the two substances given separately,
- *Additive* – when the response is equal to the sum of the response to the two substances given separately,
- *Synergistic* – when the response is greater than the sum of the response to the two substances given separately.

6.2 Determining the nature of the interaction is straightforward when both substances show a linear log dose-response relationship. It becomes more complicated when the dose-response relationships are non-linear and when there are additional confounding factors (such as the effect of exercise on airway function in asthmatic patients inhaling pollutants).

Design of studies

6.3 Chamber studies have been used to examine the interactions with regard to pathophysiological effects, between gases (ozone, sulphur dioxide, oxides of nitrogen and carbon monoxide), between gases, acid aerosols and particles and, on occasions, the effects of exposure, under controlled conditions, to ambient air as compared with clean air. In some studies the pollutants have been given in sequence, whilst in others the effects of the pollutants given individually have been compared with the effects of a mixture of pollutants. Studies in which the effects of exposure to gaseous pollutants on the response to aeroallergens were investigated are not considered here, they have been covered in detail in Chapter 5.

6.4 General points regarding the value and limitations of chamber studies have been made in previous reports of the Advisory Group,[1-3] particularly in the report on 'Sulphur Dioxide, Acid Aerosols and Particulates'.[2]

Sequential studies

6.5 In sequential studies subjects have been exposed to one pollutant for a variable period followed immediately, or after an interval, by exposure to a second pollutant. The design has varied between studies but in general there has been at least one additional control day on which subjects were exposed to clean air followed by the second pollutant given under identical conditions. In general, subjects have been blind to the pollutant to which they were being exposed. Details of individual studies are given in Annex 6A. In some instances the sequence has mimicked the pattern of exposure that might be expected to occur out of doors; exposure to a nitric acid (HNO_3) aerosol followed by ozone (O_3), for example, simulates the sequence of acidic morning fog followed by high levels of O_3 in the afternoon and evening that occurs in southern California.[4] The studies are discussed here according to the first pollutant to which subjects were exposed.

Ozone

6.6 The effects of exposure to O_3 on the response to sulphuric acid (H_2SO_4) and sulphur dioxide (SO_2) have been investigated in two studies.[5,6] In the first, exposure of healthy subjects to O_3 (300 ppb, 600 $\mu g/m^3$, for 2 hours), followed immediately by exposure to H_2SO_4 (100 $\mu g/m^3$ for 4 hours) did not cause any change in lung function or bronchial reactivity to methacholine.[5] There was also no change in lung function following exposure to either pollutant alone on separate days. In the second study, by Koenig *et al.*,[6] in adolescent asthmatics, the fall in FEV_1 (8%) was greater after exposure to O_3 (120 ppb,

240 $\mu g/m^3$, for 45 mins) followed immediately afterwards by SO_2 (100 ppb, 286 $\mu g/m^3$) than following exposure to clean air followed by SO_2 (3% fall in FEV_1) or to O_3 followed by O_3 (2% fall in FEV_1).

6.7 The lack of response to O_3 in the study by Kulle *et al.*[5] is perhaps surprising, suggesting that the subjects were relatively O_3-insensitive,[1] though the amount of exercise carried out during the study was fairly light.[5] The adolescent asthmatic patients studied by Koenig *et al.* showed a small response to O_3 and, as would be expected, a response to SO_2;[6] the study was better able, therefore, to detect an interaction although it was small. The changes are too small to say with confidence whether the interaction was additive or synergistic.

Oxides of nitrogen

6.8 Two studies on the effect of NO_2 on the response to SO_2 in subjects with asthma have come to different conclusions. Exposure to NO_2 (300 ppb, 564 $\mu g/m^3$ for 30 mins) did not increase the airway response to SO_2 (up to 4000 ppb, 11,400 $\mu g/m^3$) one hour later.[7] In a second study however, exposure to NO_2 (250 ppb, 470 $\mu g/m^3$ for 30 minutes) increased the airway responsiveness to SO_2 (750 ppb, 2145 $\mu g/m^3$) administered 15 minutes later, although it had no effect on resting airway function.[8]

6.9 The reason for the different effects of NO_2 on the response to subsequent exposure to SO_2 in the two studies is not clear. The main difference between the studies is that the study showing a positive interaction had a larger number of subjects, measured the SO_2 response 15 minutes rather than 60 minutes after completing the NO_2 exposure and did not include exercise. Effects from exposure to NO_2 have been reported more frequently in chamber studies in which subjects do not exercise, though the explanation for this remains obscure (see reference 3).

6.10 In a recent study by Hazucha *et al.*[9] the fall in FEV_1 following exposure to O_3 (300 ppb for 2 hours) was slightly but significantly greater when the subjects had been exposed 3 hours previously to NO_2 (600 ppb for 2 hours) rather than to clean air. The falls in FEV_1 and FVC with clean air followed by O_3 were 7 and 10% compared to falls of 8.5 and 12% for NO_2 followed by O_3. The response to methacholine was increased to a greater extent following exposure to NO_2 and O_3 compared with air and O_3.

Acid aerosols

6.11 The effect of nitric acid given as a fog on the response to O_3 was compared with the effect of H_2O fog and clean air in 39 O_3-sensitive asthmatic patients by Aris *et al.*[4] Exposure to either HNO_3 fog (0.5 mg/ml) or H_2O fog for 2 hours *reduced* the subsequent response to O_3 (200 ppb, given 1 hour later for 3 hours, with exercise) when compared to the effect of clean air followed by O_3. There was no difference between the effects of HNO_3 and H_2O fog.

6.12 Since both fogs rendered patients less susceptible to O_3 the protective effect is presumably due to the fog rather than the nitric acid. The development of refractoriness (reduced response to the same bronchoconstrictor challenge) is well recognised in asthmatic patients after inhalation of H_2O fog and after exercise. The cause of refractoriness is not certain but it appears to be due to release of an inhibitory prostanoid.[10] The subjects studied by Aris *et al.*[4] were O_3-sensitive but healthy and, although not asthmatic, they were more reactive to methacholine than many non-asthmatic subjects. The data suggest that the fog made them refractory to the effects of O_3.

6.13 A study of the effect of prior exposure to H_2SO_4 (100 $\mu g/m^3$) or NaCl aerosol for 3 hours on the response, 24 hours later, to O_3 (for 3 hours; 80, 120 or 180 ppb; 160, 240 or 360 $\mu g/m^3$, respectively) in healthy and asthmatic subjects has been reported.[11] There was no direct effect on lung function of exposure to the acid aerosol in either group and no response to O_3, or O_3 preceded by H_2SO_4, in the healthy group. Pre-exposure to H_2SO_4 increased the fall in FVC in response to 180 ppb O_3 in the asthmatic subjects from 3.6% to 6.8% compared to NaCl. The reductions in FVC and FEV_1 in the asthmatic subjects were variable but there was evidence for an interaction between acid aerosol and O_3 exposures both immediately and 4 hours after the latter exposure.

Combination studies

6.14 Combination studies are divided into:

(i) those that compared the response to individual pollutant gases and their combinations, and

(ii) those that compared the response to gases with and without the addition of acid particles, fogs or particulate material.

Studies of pollutant gases

6.15 In these studies the effects of combined exposure to two or more pollutant gases have usually been compared with the effects of exposure to one or more of the gases studied separately though under identical conditions, with the subjects blind to the nature of the gas being inhaled. Details of individual studies are given in Annex 6B. Some of the early studies involved a very small number of subjects and some combined the findings in asthmatic and non-asthmatic subjects. Some studies have used historical control data and have not studied the effect of single pollutants in the same subjects.[12-15]

6.16 The effects of combining very high concentrations of NO_2 and SO_2 were studied in two early investigations, published in 1967 and 1979. There was evidence only of an additive effect between NO_2 and SO_2 (both at concentrations of 2500 ppb for 10 mins) in the study by Abe.[16] In a study by von Nieding *et al.*[17] subjects were exposed for 2 hours to mixtures containing NO_2, SO_2 and O_3 at either low (53 ppb, 100 $\mu g/m^3$; 105 ppb, 300 $\mu g/m^3$; 25 ppb, 50 $\mu g/m^3$; respectively) or high (5000 ppb, 9400 $\mu g/m^3$; 5000 ppb, 14,300 $\mu g/m^3$; 100 ppb, 200 $\mu g/m^3$; respectively) concentrations. These combinations were compared with exposures to control air, the individual gases or combinations of NO_2 with either SO_2 or O_3. Exposure to the high concentration $NO_2/SO_2/O_3$ mixture did not alter airway resistance or arterial oxygen tension to a greater extent than did NO_2 alone. There was no effect of the low concentration ternary mixture on these two measures. Bronchial reactivity to acetylcholine increased, as compared with the control exposure, after exposure to the $NO_2/SO_2/O_3$ gas combination at low concentrations and to a slightly greater extent after the high concentrations, although the difference in response to the low and high concentration combinations was small.[17]

6.17 Several studies have examined the effects of low concentrations of pollutant gases, generally in the high ambient range or slightly above.[12-15,18-21] In the studies involving O_3 there has usually been a small response to O_3 which was no greater when subjects breathed the same concentration of O_3 plus NO_2[18-21] or NO_2 with carbon monoxide (CO).[18,19] In one study by Islam and Ulmer[12] a combination of SO_2, NO_2 and O_3 (5000 ppb, 14,300 $\mu g/m^3$; 5000 ppb, 9400 $\mu g/m^3$; 100 ppb, 200 $\mu g/m^3$ respectively) caused a small fall in oxygen tension and an increase in airways resistance which the authors thought was consistent with an effect of O_3 alone, although the effect of O_3 alone was not measured. In a further study by these authors[13] there was no change in lung function after inhalation of a combination of the same gases (SO_2: 315 ppb, 900 $\mu g/m^3$; NO_2: 160 ppb, 300 $\mu g/m^3$; O_3: 75 ppb, 150 $\mu g/m^3$) for 8 hours on each of 4 consecutive days. In the most recent study Adams *et al.*[21] found no difference in the reduction of indices of lung function after exposure to O_3 (300 ppb, 600 $\mu g/m^3$) or O_3 (300 ppb) plus NO_2 (600 ppb, 1128 $\mu g/m^3$) for one hour with heavy exercise in 40 young healthy subjects.

6.18 Linn *et al.*[14] studied the effect of a combination of NO_2 (500 ppb, 940 $\mu g/m^3$) plus SO_2 in healthy and asthmatic subjects (SO_2 concentrations 500 ppb, 14,300 $\mu g/m^3$ and 300 ppb, 858 $\mu g/m^3$ respectively) and found no change in lung function in either group when compared to clean air exposure. There was a small increase in reported symptoms following exposure to the combination of gases compared to clean air in normal subjects and, later in the day, in asthmatic patients. These increases were statistically significant although the increase was non-specific with regard to any one symptom. Whether this was due to an interaction is uncertain since the effects of NO_2 and SO_2 alone were not studied.

6.19 In general, the studies of gas combinations have shown, at most, an additive effect and none has found any evidence of a synergistic effect. The studies that have shown a

clear response to O_3 alone have not shown a greater response when O_3 was combined with NO_2, SO_2 or CO. Most studies have been carried out in non-asthmatic subjects. There were no significant differences in the response to NO_2 (500 ppb, 940 $\mu g/m^3$) plus SO_2 in normal and asthmatic subjects when studied in the same way by Linn *et al.*,[14] although the asthmatic subjects were exposed to a lower SO_2 concentration (300 ppb, 858 $\mu g/m^3$) than the normal subjects (500 ppb, 1430 $\mu g/m^3$).

Studies of gases, acids and particles

6.20 The studies of mixtures of gases, acid aerosols and particles are generally similar in design to the studies of gases outlined above. They have included various combinations of gases plus acid aerosols (H_2SO_4, HNO_3), sulphates, peroxyacetyl nitrate (PAN) and particles (plastic dust ± vanadium coating, activated carbon). Details of individual studies are given in Annex 6C.

6.21 In the studies that included O_3 this invariably had the dominant effect. There has usually been little response to co-pollutants such as H_2SO_4 when these were given alone. Therefore any interaction would be seen as a greater response to the combination of O_3 and the co-pollutant as compared with the response to O_3 alone. In most studies the response to O_3 was not increased significantly when it was given with co-pollutants, which included PAN and NO_2,[22] HNO_3,[23] H_2SO_4,[24] and H_2SO_4, NO_2 or SO_2.[25] In the study by Stacy *et al.* the response to O_3 plus H_2SO_4 and O_3 plus NH_4HSO_4 was slightly greater than the response to O_3 alone but the difference was not statistically significant.[25] A small fall in FEV_1 was seen following a combination of O_3 (370 ppb, 740 $\mu g/m^3$), SO_2 (370 ppb, 1058 $\mu g/m^3$) and H_2SO_4 (100 $\mu g/m^3$) in a study by Kleinman *et al.*[26] but the component gases were not studied separately so whether an interaction occurred is uncertain although the magnitude of response is similar to that expected from O_3 alone. A study by Koenig *et al.*,[27] in adolescents with asthma, did not demonstrate any significant changes in lung function after exposure to oxidant gases (O_3 plus NO_2) with or without either H_2SO_4 or HNO_3. The authors suggest[27] that the 90 minute exposure period used in this study was too long and refer to an earlier study[28] from their laboratory in which effects of acid aerosols had been detected after a 45 minute exposure but not after one lasting 90 minutes.

6.22 A recent study by Linn *et al.*[29] is of particular interest since it examined the repeatability of the demonstrated interaction between O_3 and H_2SO_4 within subjects. In the initial study 15 healthy and 30 asthmatic subjects inhaled O_3 (120 ppb, 240$\mu g/m^3$) or H_2SO_4 (100 $\mu g/m^3$) or the combination for 6.5 hours a day on two successive days a week apart. Exposure to H_2SO_4 alone had no effect, whilst O_3 alone caused a small but significant reduction in lung function (mean fall in FEV_1 = 60 and 220 ml in normal and asthmatic subjects, respectively). The findings were greater on the first than on the second exposure day, though the difference was not statistically significant. FEV_1 fell more in asthmatic patients on all study days (due to exercise-induced bronchoconstriction); the FEV_1 decrement attributable to O_3 did not differ significantly, however, between asthmatic and non-asthmatic subjects. When O_3 was combined with H_2SO_4 the decrement in lung function was increased and the difference from the O_3-alone day was of borderline statistical significance in both groups (on average a fall in FEV_1 of 100 ml could be attributable to O_3 and a fall of 189 ml to $O_3 + H_2SO_4$). The authors then restudied 11 subjects (10 asthma, 1 healthy) with a greater than average response to $O_3 + H_2SO_4$ compared to O_3 alone. On repeat testing the response to the combination of pollutants continued to be greater than the response to O_3 alone. The effects appeared to be additive rather than synergistic.

6.23 The response to SO_2 was not changed when it was inhaled with inert or vanadium-coated plastic dust (aerodynamic diameter 2.2-15 µm) though only 27% by weight of the particles had diameters less than 8.9 µm[30] or activated carbon (mass median diameter 1.5 µm)[31] (see Annex 6D). There was no significant difference in the response of healthy subjects to NO_2 (510 ppb, 959 $\mu g/m^3$) plus SO_2 (500 ppb, 1430 $\mu g/m^3$) plus sodium chloride and zinc ammonium sulphate aerosols (332 and 25.8 $\mu g/m^3$, respectively) for 2.25 hours compared to exposure to sodium chloride aerosol alone.[32]

6.24 Bronchial biopsy and bronchoalveolar lavage were carried out by Aris *et al.*[23] in

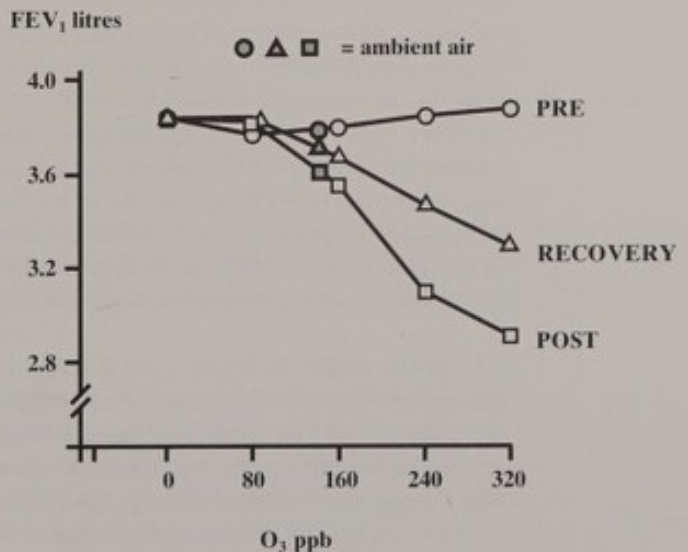
healthy subjects after exposure for 4 hours to clean air or HNO_3 or, in a separate experiment, after exposure to $HNO_3 + O_3$ or O_3 alone. There was no difference in cellular (total cells, and percentage of neutrophils, eosinophils, lymphocytes, macrophages and epithelial cells) or biochemical (total protein, albumen, fibronectin and α_1-antitrypsin) constituents of bronchoalveolar lavage and no difference in bronchial biopsy findings between clean air and nitric acid or between O_3 with and without nitric acid.

Studies of ambient air in exposure chambers

6.25 The effects of exposure to ambient air have been compared with the effects of exposure to clean air under controlled chamber conditions. Five of the six studies are from Los Angeles. The level of pollutant gases in ambient air varied considerably between studies. Details of the individual studies are given in Annex 6D.

6.26 The first study from Los Angeles compared the response to exposure for 2 hours with light exercise to ambient Los Angeles air with that of exposure to clean air in 34 healthy and 30 asthmatic subjects.[33] Ambient levels of O_3 were high (218 ppb, 436 $\mu g/m^3$) at the time of the study and both normal and asthmatic subjects showed a small reduction in lung function compared to clean air. There was no exposure to O_3 alone to determine the extent to which the effects of ambient air could be accounted for by the high O_3 concentration. This problem was remedied in a second study from Los Angeles[34] in which 50 competitive cyclists were studied on 6 occasions after inhaling either clean air or O_3 (80, 160, 240 or 320 ppb; 160, 320, 480, or 640 $\mu g/m^3$) or ambient polluted air (mean O_3 concentration 153 ppb, 306 $\mu g/m^3$; mean concentrations of other pollutants: SO_2 6 ppb, 16 $\mu g/m^3$; NO_2 40 ppb, 75 $\mu g/m^3$; CO 2200 ppb, 2750 $\mu g/m^3$; TSP 295 $\mu g/m^3$), for 1 hour with vigorous exercise (additional exposure time in the chamber included a 10 min warm up period and, after the 1-hour exercise period, a 5 min cool down period and 5 min of lung function testing). Ozone produced a dose-related fall in FEV_1 and FVC with a mean maximum fall of around 1 liter for both measurements at the highest concentration of O_3 (320 ppb, 640 $\mu g/m^3$). Ambient air produced the same effects as the equivalent level of O_3, suggesting that all the effects of ambient air could be attributed to O_3 (see Figure 6.1).

Figure 6.1 **Mean FEV_1 values of 50 volunteers before (PRE) and immediately after (POST) exposure, with heavy exercise, to different concentrations of O_3 for 1 hour on separate days. The mean FEV_1 measured during the recovery phase (RECOVERY, after a 1 hour exposure to filtered air) is also shown. The solid symbols show the change in FEV_1 following inhalation of ambient air (O_3 concentration 153 ppb) by the same subjects studied under identical conditions. The change with ambient air was almost identical to that seen with a similar concentration of O_3, suggesting that the effects of ambient air were largely due to O_3 (data from Avol *et al.*,[34] redrawn with permission).**



6.27 In a further study[35] the pollutant levels on the ambient air study days were relatively low (NO_2: 86±24 ppb, 162±45 µg/m^3; O_3: 29±10 ppb, 58±20 µg/m^3; SO_X: 4±1 ppb, 11±3 µg/m^3). The fall in lung function of asthmatic subjects was greatest with ambient air but did not differ significantly from the change seen following exposure to clean air or NO_2 (300 or 600 ppb, 564 or 1128 µg/m^3) on separate days. In a subsequent study of 34 adolescents,[36] NO_2 levels in ambient air were 90 ppb (169 µg/m^3). When compared to exposure to clean air there was no effect from the Los Angeles air, whereas there was some response, of borderline statistical significance, to exposure to NO_2 (300 ppb, 564 µg/m^3); interpretation is complicated as subjects had worse symptoms before exposure to NO_2.

6.28 In a study from China,[37] 105 breaths of polluted air (SO_2: 70-120 ppb, 200-343 µg/m^3; NO_2: 450-500 ppb, 846-940 µg/m^3) did not alter airway function or the response to methacholine or allergen in six children sensitive to house dust mite.

6.29 Thus, the three studies which found a significant fall in lung function with exposure to ambient air were the three from Los Angeles carried out when the ambient concentration of O_3 was over 150 ppb (300 µg/m^3).[33,34,38] The 1984 study[34] is particularly interesting as it suggests that most, if not all, of the response to ambient air seen with vigorous exercise in the competitive cyclists was due to O_3.

6.30 Studies of exposure to ambient air under controlled conditions provide a useful bridge between chamber and epidemiological studies. Ideally, sensitive subjects should be studied on high pollution days and their response compared with that to the same concentrations of component gases on a separate occasion, as in the study by Avol *et al.*[34] Other studies, in other parts of the world, are needed to confirm whether the response to ambient air can be explained by O_3 alone or whether there is evidence of a synergistic interaction between pollutant gases or a rôle for other constituents of ambient air such as particles. Carrying out such experiments is difficult because of the unpredictable nature of episodes of high pollution.

6.31 One important question with studies of ambient air concerns the time at which the exposures to clean air or the combinations of component gases should be carried out. If they are carried out when ambient pollution levels are high, the prior exposure to high levels of pollutants is likely to affect the response to the clean air which is usually breathed for a few hours only (a maximum of 3 hours in these studies). In the study by Linn *et al.*[33] exposure to clean air was carried out when peak ambient O_3 concentrations were 209 ppb (418 µg/m^3), as compared to 305 ppb (610 µg/m^3) on the ambient air study day. The extent to which this prior exposure to ambient air containing O_3 would modify the response to clean air is uncertain but it is likely to reduce any differences in response between clean air and polluted air in chamber studies.

Summary

6.32 Several of the sequential studies have shown a greater response to a second pollutant following prior exposure to another pollutant (O_3, NO_2 or H_2SO_4) rather than to clean air although the results have been variable. Ozone enhanced the response to SO_2 in adolescent asthmatics[6] but had no effect on the response to H_2SO_4 in another study.[5] Exposure to NO_2 enhanced the response to O_3 in one study[9] and the response to SO_2 was increased following NO_2 in one study[8] but not in a similar study.[7] Nitric acid and water fogs protected subjects against the response to O_3,[4] whilst exposure to H_2SO_4 may increase the response to O_3.[11] When an increased response has been seen it has been small. This makes it difficult to determine the nature of the interaction but there is no clear evidence of a synergistic interaction between any of the pollutants.

6.33 In the studies in which several pollutant gases are given together (O_3, NO_2, SO_2, CO and PAN) there is no evidence to suggest that the combination produces a greater effect than would be expected from summation of the responses to individual gases. In several studies none of the gases, whether given separately or together, caused a response. When a response has been seen O_3 has usually had a dominant effect. Adding NO_2, SO_2 or CO to O_3 has not enhanced the response to O_3.

6.34 The response to acids (H_2SO_4 or HNO_3) was not affected by concomitant exposure to O_3 in most studies. A recent, large study found a small additive effect between O_3 and H_2SO_4, of borderline statistical significance.[29] The finding was confirmed, however, in subjects selected because they showed an interaction on the first occasion, suggesting that an additive interaction was being detected in these subjects.

6.35 Studies of ambient air exposure in a chamber are limited; the levels of pollutants were low in one study[35] and the duration of exposure was very short in another.[37] There was a reduction in lung function in the three studies[33,34,38] when ambient air contained high O_3 concentrations and the fall in lung function with ambient air was similar to that seen with the same concentration of O_3 alone on a separate day of one of the studies.[34] These data suggest that, in Los Angeles at least, O_3 is the major contributor to the effects of ambient air on lung function. Interpretation of ambient air exposure studies is complicated by the variable ambient exposure to pollutants prior to the relatively short exposure to clean air in the chamber.

Interpretation of chamber studies involving interactions of air pollutants

6.36 Most of the chamber studies have found at most an additive effect between pollutants and no evidence of synergism or potentiation. Certain methodological points need to be considered before reaching conclusions on the significance of these findings.

- Chamber studies are difficult to carry out and studies looking at the interaction of different pollutants are more difficult than studies of a single pollutant. All outcome measures are subject to some variability or 'noise' and the more pollutants that are studied the more difficult it is to detect a small signal. A larger number of subjects needs to be studied, particularly when O_3 is involved since the response varies considerably between healthy subjects. As can be seen from the annexes many of the early studies involved a small number of subjects.

- The chances of detecting an interaction between two pollutants are greater if a measurable response can be detected from the individual pollutants when given alone. The lack of a response to a combination of pollutants at concentrations that do not individually produce a response does not exclude an interaction at higher concentrations. By analogy with pharmacological studies, the best way to look for an interaction is to determine a dose-response curve for one pollutant following exposure to a second pollutant (ideally using different concentrations of the second pollutant on different days). This clearly would be very difficult for pollutant gases – but small interactions could well have been missed because of limitations of experimental design.

- Some studies have looked at the effects of sequential exposures to pollutants, whilst others have compared the responses to mixtures of pollutant gases with those to one or more of the component pollutants. Both may be relevant to ambient conditions. If anything, the sequential study design has provided more evidence of additive effects than combination studies. This is probably due to the particular pollutants and concentrations studied, though it is possible that chemical reactions between the co-pollutants have occurred in the combination studies prior to or during inhalation, thus modifying the effect on the airways.

- The possible permutations in the combinations and concentrations of pollutants, and timing of exposures that could be studied are clearly enormous. Lack of an interaction in one set of circumstances does not exclude an interaction under other circumstances.

- Most studies have been of short duration. The effects of the ambient concentrations of pollutants experienced prior to exposure in the chamber are likely to have an important modifying effect on the chamber studies. It is impossible to standardise this and difficult to account for it in the analysis. This may explain why chamber studies from Los Angeles in general appear to show fewer positive findings than those from some other centres. Subjects show tolerance to the effects of O_3 if inhaled over several days and this is an additional complicating factor.

- Most interaction studies have been carried out on healthy subjects. Some of the studies that have shown an interaction have been in patients with asthma. No clear difference has emerged in the few studies that have compared interactions between the two groups however. If the asthmatic subjects studied had a greater response to a pollutant such as SO_2 it might be easier to identify an interaction.

- Patients with severe or brittle asthma have not been studied specifically.

- Very few studies have attempted to look at the interaction of gases with particles. Because of the diverse nature of particulate material it would be extremely difficult to do this in a systematic manner.

Conclusions

6.37 Some studies, mainly the more recent ones that have involved a larger number of subjects, have shown small interactions between pollutants which, so far, are consistent with an additive effect. There is no evidence of important synergistic interactions or potentiation between the pollutants that have been studied. The pollutants that have shown an additive effect include H_2SO_4 and O_3, O_3 followed by SO_2, and NO_2 followed by SO_2 and possibly O_3. The only study to show an antagonistic or negative interaction was one in which HNO_3 fog was inhaled prior to O_3, though the protection afforded by HNO_3 was probably related to the fog rather than HNO_3 as such. Interactions may have been underestimated due to the small size of studies, low concentrations of pollutants studied, limited duration of exposure and the confounding effects of prior exposure to ambient pollutants.

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Controlled studies of the effects of sequential exposures to air pollutants

Study	Effects studied	Subjects	1st Exposure	2nd Exposure	Outcome
Kulle *et al.* 1982[5]	O_3 on H_2SO_4	12 healthy non-smokers	Ozone (300 ppb) for 2 hours + exercise for second hour (also O_3 alone and H_2SO_4 alone on separate days)	H_2SO_4 (100 µg/m^3) for 4 hours immediately after, + exercise for last hour	No change in lung function or PD_{35} sGaw methacholine with individual or combined pollutants
Koenig *et al.* 1990[6]	O_3 on SO_2	13 adolescents with asthma (age 12-18)	Clean air or O_3 (120 ppb) for 45 min with exercise	O_3 (120 ppb) or SO_2 (100 ppb) for 15 min immediately after, + exercise	O_3-SO_2 exposure caused greater fall in FEV_1 (8%) than O_3-O_3 (2%) or air-SO_2 (3%)
Rubinstein *et al.* 1990[7]	NO_2 on SO_2	9 stable asthma	NO_2 (300 ppb) or air for 30 min, mild exercise for 20 min	SO_2 dose-response study (250 to 4000 ppb), 1 hour later	NO_2 – no effect; no change in response to SO_2
Jörres *et al.* 1990[8,39]*	NO_2 or SO_2 on isocapnic hyperventilation ± SO_2	14 non-smokers mild asthma	Filtered air, NO_2 (250 ppb) or SO_2 (500 ppb) for 30 min at rest	Isocapnic hyperventilation with SO_2 (750 ppb) or filtered air 15 min later	NO_2 and SO_2 alone – no change in sRaw. PC_{100} sRaw SO_2 slightly lower after NO_2 than after air or SO_2: no difference in PV_{100} sRaw
Aris *et al.* 1991[4]	H_2O or HNO_3 fog on O_3	39 O_3-sensitive subjects (non-asthmatic)	HNO_3 fog (0.5 mg/ml) H_2O fog or clean air for 2 hours with exercise	After one hour – O_3 (200 ppb) for 3 hours with exercise	Response to O_3 *reduced* by pretreatment with either fog. No differences between HNO_3 and H_2O fog. Subjects fairly sensitive to methacholine
Utell *et al.* 1994[11]	H_2SO_4 on O_3	30 healthy 30 asthma	H_2SO_4 (107 µg/m^3) or NaCl (105 µg/m^3) for 3 h with exercise so that ventilation quadrupled	After 24 hours – O_3 (80, 120 or 180 ppb) with exercise; incomplete block design	No effect in healthy subjects. H_2SO_4 enhanced O_3 effect at highest O_3 concentration only in asthmatics
Hazucha *et al.* 1994[9]	NO_2 on O_3	21 healthy young women	NO_2 (600 ppb) for 2 hours	O_3 (300 ppb) for 2 hours, 3 hours later, with exercise	NO_2 alone – no effect but fall in lung function after O_3 greater following NO_2 than air; response to methacholine increased after NO_2 + O_3 compared to air + O_3

* published twice – slight differences in data presented[8,39]

Abbreviations: BAL = bronchoalveolar lavage, FEV_1 = volume of air expired during the first second of a maximal or "forced" expiration, FVC = forced vital capacity, NA = not applicable, PAN = peroxyacetyl nitrate, PaO_2 = arterial oxygen tension, PC_{100} sRaw = provocative concentration causing a 100% increase in specific airway resistance, PD_{35} sGaw = provocative dose causing a 35% fall in specific airway conductance, PV_{100} sRaw = provocative ventilation causing a 100% increase in specific airway resistance, Raw = airway resistance, sGaw = specific airway conductance, sRaw = specific airway resistance, TLC = total lung capacity, TSP = total suspended particles

Conversion factors: 1 ppb NO_2 = 1.88 µg/m^3; 1 ppb O_3 = 2.00 µg/m^3; 1 ppb SO_2 = 2.86 µg/m^3; 1 ppb CO = 1.15 µg/m^3; 1 ppb HNO_3 = 2.62 µg/m^3

Annex 6B

Controlled studies of the effects of exposure to combinations of air pollutants (gases only)

Study	Subjects	Exposure	Outcome
Abe 1967[16]	5 men	NO_2 (4000-5000 ppb)	SO_2 – immediate increase in Raw
		SO_2 (4000-5000 ppb)	NO_2 – delayed increase in Raw
		$NO_2 + SO_2$ each at 2500 ppb. 10 min at rest	Mixture gave intermediate results
Hackney *et al.* 1975[59]	4 healthy	O_3 (500 ppb)	Fall in lung function after O_3 in 4 subjects with asthma, no additional effect from
	4 mild asthma	above + NO_2 (300 ppb)	NO_2 or CO. No consistent changes in 4 healthy subjects
	(hyperreactive airways)	above + CO (30,000 ppb) for 2 or 4 hours on 2 consecutive days 1 week apart	
Hackney *et al.* 1975[18]	7 healthy subjects	O_3 (500 ppb)	Fall in lung function, more marked on day 2; considerable variation between subjects
	4 subjects	a) O_3 (250 ppb)	Small effect with O_3 – no increase when NO_2 or NO_2 + CO added
	(2 asthma)	b) above + NO_2 (290 ppb) above + CO (30,000 ppb) all for 2 hours on 2 consecutive days 1 week apart (+ exercise)	
	4 subjects	a) NO_2 (290 ppb)	As above
	(2 asthma)	O_3 (500 ppb)	
		b) NO_2 (290 ppb) + O_3 (500 ppb) + CO (30,000 ppb) exposed for 2 hours on 2 consecutive days + exercise	
von Nieding *et al.* 1979[17]	11 healthy men	NO_2 (500 ppb)	The combination of gases showed no greater effect than NO_2 alone (increase in Raw, fall in PaO_2).
		SO_2 (5000 ppb)	Bronchial reactivity to acetylcholine slightly greater after combination of all 3 gases at low
		O_3 (100 ppb)	concentrations and slightly more at high concentrations compared to clean air
		clean air	
		also $NO_2 + SO_2$,	
		$NO_2 + O_3$, $NO_2 + SO_2 + O_3$	
		at concentrations above, also at	
		low levels (53, 105, 25 ppb) for	
		2 hours + light exercise	
Islam and Ulmer 1979[12]	24 healthy subjects	Room air or	Increase in Raw and fall in PaO_2 with mixture, slightly greater with exercise. The authors
		SO_2 (5000 ppb) +	conclude that there is no potentiation; no control single gas exposure in this study
		NO_2 (5000 ppb) +	
		O_3 (100 ppb)	
		± light exercise for 2 hours	

Annex 6B (continued)

Controlled studies of the effects of exposure to combinations of air pollutants (gases only)

Study	Subjects	Exposure	Outcome
Islam and Ulmer 1979[13]	15 healthy men in total; studies on groups of 5	SO_2 (315 ppb) + NO_2 (160 ppb) + O_3 (75 ppb) for 8 hours on 4 days + clean air on day before or day after. No exercise	No change in Raw, arterial blood gas tensions or airway response to acetylcholine
Linn *et al.* 1980[14]	24 healthy 19 asthma	clean air or NO_2 (500 ppb) + SO_2 (500 ppb healthy) or (300 ppb asthma) for 2 hours with exercise	No difference in lung function between exposures in either group. After NO_2 and SO_2 symptoms increased in healthy subjects, and later in the day in asthmatic patients.
Folinsbee *et al.* 1981[15]	8 healthy young men (1 allergic, 1 sensitive to smog)	clean air or NO_2 (500 ppb) + O_3 (500 ppb) varying temperature and humidity 2 hours + exercise	Fall in FEV_1 with $NO_2 + O_3$; not altered by changing temperature and humidity. Changes no different from historic data on O_3 alone
Kagawa 1983[20]	7 healthy men	clean air O_3 (150 ppb) SO_2 (150 ppb) NO_2 (150 ppb) $O_3 + SO_2$, $O_3 + NO_2$, $NO_2 + SO_2$ and $O_3 + SO_2 + NO_2$	Small changes in sGaw, FVC or FEV_1 mainly with O_3; no significant enhancement when pollutants were combined
Adams *et al.* 1987[21]	40 young adults (trained)	NO_2 (600 ppb) O_3 (300 ppb) clean air $NO_2 + O_3$ for 1 hour + exercise	No change in FEV_1, sRaw etc with NO_2 alone; similar fall in FEV_1 with O_3 (22%) and $NO_2 + O_3$ (22%)

For abbreviations and conversion factors see footnotes to Annex 6A

Annex 6C

Controlled studies of the effects of exposure to combinations of air pollutants (gases + acid aerosols or particles)

Study	Subjects	Exposure	Particle Size	Outcome
Andersen *et al.* 1981[30]	16 healthy young subjects	clean air	27% by weight	No change in FEV_1.
		SO_2 (2.6 or 13 mg/m^3) alone or + inert plastic dust (2 or 10 mg/m^3) or SO_2 + vanadium-coated dust (10 mg/m^3) for 5 hours	< 9 µm	No synergistic effects
Kleinman *et al.* 1981[26]	19 healthy subjects	clean air or	0.5 µm mass	FEV_1 fell 3.7%.
		O_3 (370 ppb) +	mean aerodynamic	No control with O_3 alone so difficult to interpret
		SO_2 (370 ppb) +	diameter	
		H_2SO_4 (100 µg/m^3) for 2 hours with exercise		
Stacy *et al.* 1983[25]	9-15 healthy men per group	SO_2 (750 ppb)	0.55 µm mass median	Only O_3 caused changes in lung function.
	(231 men in total in 19 groups)	NO_2 (500 ppb)	diameter for all chemical	No clear additive effect with H_2SO_4
	aged 18–40 years	O_3 (400 ppb)	species	(fall in FEV_1 11% *v* 8% for O_3 alone in different subjects)
		H_2SO_4 (100 µg/m^3)		
		$(NH_4)_2SO_4$ (133 µg/m^3)		
		NH_4HSO_4 (116 µg/m^3)		
		NH_4NO_3 (80 µg/m^3)		
		the above in various combinations clean air for 4 hours with exercise		
Kleinman *et al.* 1985[32]	20 healthy subjects	NaCl ± zinc ammonium sulphate (25 µg/m^3)	TSP – 1.1µm	No difference in lung function: symptoms slightly
		NO_2 (500 ppb) + SO_2 (500 ppb) for 2.25 hours with exercise	NaCl – 1.1 µm	greater with pollutant exposure but not statistically significant
			$Zn(NH_4)_2(SO_4)_2$ – 1.3µm	
Kulle *et al.* 1986[31]	20 healthy men	SO_2 (1000 ppb) ± activated carbon (0.5 mg/m^3) for 4 hours + exercise	1.5 µm mass median diameter	Some irritant effects and small fall in lung function no difference between SO_2 and SO_2 + activated carbon
Horvath *et al.* 1987[24]	9 healthy men	O_3 (250 ppb)	< 0.05 µm mass median	No change in lung function with either pollutant or with combination
		H_2SO_4 (12-1600 µg/m^3) singly and together for 2 hours with exercise	diameter	
Drechsler-Parks *et al.* 1989[22]	16 young (18-26 years)	clean air	NA	Young subjects showed large response to O_3, PAN
	and 16 older (51-76 years)	O_3 (450 pbb)		and NO_2 did not alter this reponse significantly.
	healthy non-smokers	O_3 (450 ppb) + PAN (130 ppb)		Older subjects had smaller responses generally; again
		O_3 (450 ppb) + NO_2 (600 ppb)		not increased significantly by NO_2 and PAN
		NO_2 + O_3 + PAN 2 hours + exercise		

Controlled studies of the effects of exposure to combinations of air pollutants (gases + acid aerosols or particles)

Study	Subjects	Exposure	Particle Size	Outcome
Aris 1993 *et al.*[25]	2 studies – both 10 healthy subjects	a) clean air or HNO_3 (500 µg/m^3) b) O_3 (200 ppb) alone or + HNO_3 (500 µg/m^3) for 4 hours with exercise	NA	No difference in lung function or BAL findings between HNO_3 and air or between O_3 and O_3 + HNO_3
Linn 1994[29]	15 normal/atopic 30 asthma	clean air or O_3 (120 ppb) H_2SO_4 (100 µg/m^3) and O_3 + H_2SO_4; each on 2 successive days for 6.5 hours/day + exercise; at weekly intervals	0.5 µm mass median aerodynamic diameter	H_2SO_4 alone – no effect; O_3 alone or with H_2SO_4 caused fall in lung function and increase in methacholine reactivity. Difference between O_3 with and without H_2SO_4 generally small and non-significant but larger in a few subjects, and this was repeatable

For abbreviations and conversion factors see footnotes to Annex 6A

Annex 6D

Effects of exposure to ambient air in chamber studies

Study	Subjects	Exposure	Outcome
Linn *et al.* 1980[33]	34 healthy 30 asthma	clean air ambient Los Angeles air (O_3 = 218, SO_2 = 12, NO_2 = 69, CO = 2900, hydrocarbons = 2600 ppb, respectively; total particles = 182, sulphate = 16, nitrate = 7 $\mu g/m^3$, respectively) for 2 hours with exercise	Small reduction in FEV_1, FVC and TLC with ambient air; no difference between normal and asthmatic subjects
Avol *et al.* 1983[34]	60 (7 with asthma) in 1980 98 (50 with asthma) in 1981	1 hour rest in clean air followed by clean air or ambient polluted air (mean O_3 = 165 ppb and 156 ppb in 1980 and 1981; TSP = 227 and 116 $\mu g/m^3$) for 1 hour with exercise	1980: 3% fall in FEV_1 and FVC with ambient exposure; no change with clean air. 1981: mean fall in FVC of 1.4% (not significant) in healthy subjects. FEV_1 no change. Asthmatics showed a fall in FEV_1 with exercise on both exposure days, the fall was greater with clean air but slower to return to normal with ambient air
Avol *et al.* 1984[34]	50 competitive cyclists (2 with mild asthma)	clean air ambient polluted air O_3 at 80, 160, 240 and 320 ppb on separate days for 1 hour with heavy exercise	There was a dose-response fall in FEV_1 and FVC with O_3 (maximum mean fall in FEV_1: 1 liter). Ambient air (mean O_3 = 153 ppb) caused a similar change to O_3 (150 ppb) on O_3 dose-response curve
Avol *et al.* 1988[35]	moderate/severe asthma n = 59 for NO_2 and clean air n = 36 for ambient air in addition	clean air NO_2 (300 and 600 ppb) Los Angeles ambient air (NO_2 = 86, O_3 = 29, SO_X = 4, hydrocarbons = 2500 ppb, respectively; particles, sulphates and nitrates = 119, 2.5 and 23 $\mu g/m^3$, respectively) 2 hours + exercise	Although changes with ambient air were greatest none was significant
Avol *et al.* 1989[36]	34 adolescent asthmatics	clean air, NO_2 (300 ppb) or Los Angeles ambient air (mean NO_2 = 90 ppb) for 3 hours + exercise	No effect from Los Angeles air; NO_2 effects equivocal as lung function and symptoms were worse *before* exposure. A fall in lung function at 1 hour only (then an increase) and increase in symptoms after 1 week only
Huang *et al.* 1991[37]	6 house dust mite sensitive children	ambient versus polluted air (NO_2 450-500 ppb SO_2 70-120 ppb) 105 breaths of air inhaled	No difference in lung function or response to methacholine or allergen between ambient and polluted air

For abbreviations and conversion factors see footnotes to Annex 6A

Chapter 7

Public Health Effects of Exposure to Ambient Pollution Mixtures

Introduction

7.1 This chapter addresses the question of whether the particular mixtures of pollution now encountered in the United Kingdom (UK) are likely to be harmful to health. Previous reports by the Advisory Group have evaluated the possible health effects of the individual pollutants ozone,[1] sulphur dioxide, acid aerosols and particulates[2] and the oxides of nitrogen[3] but noted that this approach was limited because the population is almost always exposed to mixtures of pollutants. The evidence for adverse health effects of mixed pollutants rests largely on observational studies of ambient exposure. The specific purpose of this report is to assess the likely effects of short term episodes of the types of pollution likely to occur in the UK so that responsible authorities have a sound basis for the provision of advice to the population. This chapter will therefore be confined to short term effects: reviews of long term effects may be found in previous reports of the group,[1-3] and elsewhere.[4-7]

7.2 The studies to be reviewed fall into two groups. The first are those of single (or several) episodes. These provide direct evidence about the health effects of the mixture present at the time of the episode and are directly relevant to the question of health advice during episodes. The second group are studies of daily health events where the result is a coefficient describing the relationship between health events and air pollution (controlling for confounders as appropriate). The relevance of these coefficients to predictions of the health effects of episodes depends upon the composition of the pollutant mixture. In some studies the mixture has been represented by a single index pollutant and the coefficient related to this alone. When this is done it is difficult to explain the effects in mechanistic terms. The presence or absence of a threshold in the dose-response curve is also important in making predictions of effects.

7.3 Most of the published evidence from daily time-series studies (of both panels and of whole populations) has been discussed in detail in the three previous reports of the group.[1-3] This chapter will draw on the conclusions of those reports, taking into account information from more recent studies (such as meta-analyses and reviews) not referred to in those reports. Annexes summarising the results of the newer studies are included for reference. The previous reports also described studies of episodes, but not in sufficient detail to meet the objectives of the present report; for this reason, episode studies will be reviewed in more detail and a section will be devoted to the recent analysis of the effects of the episode which occurred in London in December 1991. A detailed review of time-series studies relating to the health effects of inhaled particulate matter is currently being prepared by the Department of Health's Committee on the Medical Effects of Air Pollutants.[8]

7.4 The relevance of evidence from other countries or from earlier periods in the UK to the current and projected conditions will depend on a number of factors, the most important being: 1) the composition of the pollutant mixture in the region studied; 2) the concentrations of pollutants; and 3) whether categories of pollutants have generic effects. This third factor will, for example, require judgements as to whether particles from coal combustion have similar effects to those from motor vehicles, or whether the mechanism of toxic action of nitrogen dioxide (NO_2) is similar to that of ozone (O_3).

7.5 Whilst it is likely that different pollutants will have different biochemical and cellular effects on the lung, it is important to appreciate that, at a physiological and symptomatic level, the repertoire of lung responses is limited. Pathophysiological effects include changes in ventilation, reduced lung volume, bronchoconstriction, ventilation-perfusion imbalance, impaired gas transfer, reduced resistance to infection and impaired mucociliary clearance. Clinically, these effects could present as a worsening of

cardiorespiratory function or an increase in symptoms in those with existing disease. Symptomatically, possible manifestations of a pollution effect might be an increase in cough, breathlessness, chest tightness, wheeze, or phlegm. Thus, at the symptomatic or public health levels, the acute effects of a range of pollutants may not be very different.

Single episodes

Early studies

7.6 The two most frequently cited early studies relate to smog episodes in the Meuse Valley, Belgium[9] and in Donora, Pennsylvania.[10] Both were on a small scale in comparison with the 1952 episode in London but were distinguished by the intensity of the smog and an obvious effect on mortality in a relatively small area. The Belgian incident occurred in 1930 among the population of a small industrialised valley on the Meuse river and was associated with many reports of illness and an increase in deaths to 60, about 10 times those expected.

7.7 Similarly, Donora was a small industrial town of about 12,000 inhabitants situated in a Pennsylvania river valley bordered by hills. During a smog which developed in 1948, 20 deaths occurred, 18 of which were attributed to the fog on clinical grounds. An extensive survey of morbidity was organised soon after the event and some evidence (possibly biased by knowledge of the event) was obtained which suggested that an illness characterised by irritation of the respiratory tract and, in severe cases, dyspnoea was experienced by about 40% of the population, among whom about one quarter were described as severely affected.[10] Neither this nor the Belgian study are of much relevance to the current situation in the UK, except as a reminder of the potential for air pollution to cause adverse health effects.

London, 1945-1970: SO_2 and particles

7.8 For several centuries, the "stinking fogs", for which London was notorious, were believed to be harmful to health.[11] Scientific studies had shown them to be associated with increased mortality but it had proved difficult to separate the effects of air pollution from that of the weather.[12,13] The "Great Smog" of 1952 remains one of the episodes providing more convincing evidence that air pollution can indeed cause serious health effects.[14]

7.9 The effect of air pollution on health was established by comparing the time-series of mortality before, during, and after the smog period with that from previous years and other "Great Towns" of Great Britain. The scale of the effect was so large that it could not be sensibly attributed to any other cause. At three Central London sites, the all-sites means of the maximum levels of black smoke and SO_2 (daily average) reached during the period of December 5th-9th, 1952 were 2650 $\mu g/m^3$ and 1260 $\mu g/m^3$ (441 ppb) respectively, and the highest level of black smoke at an individual site was in excess of 4000 $\mu g/m^3$. The episode was estimated to have caused an excess of 3500 to 4000 deaths among the population of Greater London (then 8 million). This estimate was arrived at by comparing the smog period with that immediately preceding it, with the equivalent period in 1951, and with mortality in towns not affected by the smog. Of the excess deaths 80-90% were due to cardiorespiratory disease, and 60-70% were among people over the age of 65.[14]

7.10 Morbidity data derived from sickness claims and applications for admission to hospitals were incomplete but indicated that the percentage increase in morbidity was less than that observed for mortality.[14] The only primary care data were from a practice in Beckenham where there was an increase in attendances for upper and lower respiratory symptoms (usually without abnormal chest signs) in healthy persons and a worsening of symptoms in those with pre-existing lung disease. It was noted that none of the child asthmatics in the practice were adversely affected and that there was less illness than usual in children.[15]

7.11 Subsequent smog episodes in London in 1956, 1957 and 1959 were associated with evidence of excesses of 1000, 700-800 and 200-250 deaths, respectively.[16-18] The last occasion on which an association between mortality and an air pollution episode was reported was in 1962.[2] By the late 1960s, visual inspection of time-series data of morbidity indicators (derived from hospital admissions and a panel of chronic bronchitic patients from whom asthmatics were excluded) did not reveal any effects of air pollution.[19]

London and Southern England 1976: ozone

7.12 In the 1970s, it was recognised that the South East was experiencing episodes of O_3 pollution in the summer.[20] During the exceptional weather conditions of June 1976, London and the surrounding Home Counties experienced an episode of pollution during which 1-hour maximum O_3 levels reached 210 ppb (420 $\mu g/m^3$) in Central London and 258 ppb (516 $\mu g/m^3$) in the rural south (WHO guideline levels for maximum hourly average, 76-100 ppb). This was, in part, caused by the transport of precursors, including NO_2 and volatile organic compounds, from continental Europe. Analysis of air mass trajectories over western Europe confirmed this.[21] Mortality and hospital admissions rose in the South East but it has not been possible so far to separate the effects of O_3 from those of the very high temperatures at the time.[22]

Birmingham, 1992: SO_2, NO_2 and particles

7.13 In 1992, between the 17th and 27th of December, Birmingham experienced an air pollution episode during which hourly averages of SO_2 rose to 130 ppb (345 $\mu g/m^3$), of NO_2 to 207 ppb (389 $\mu g/m^3$) and of PM_{10} to 231 $\mu g/m^3$. Data collected from diaries kept by 10 "mild" and 14 "brittle" adult asthmatic patients living near the pollution monitoring stations were analysed to examine the effects of the episode.[23] The "mild" group showed no significant changes but the severe group showed evidence of adverse effects during the episode, indicated by reductions in peak flow, and increased use of medications.

London, 1991: NO_2 and particles

7.14 The results of the investigation into the effects of the air pollution episode which occurred in the four days from the 12th to 15th of December 1991 in London are very relevant to the health effects of NO_2-associated winter pollution (Type 2 episodes, see Chapter 3) and will be described in some detail. At that time, anticyclonic weather created the still and cold conditions which predispose the London basin to winter air pollution episodes. Levels of NO_2 exceeded the 1-hour WHO guideline (210 ppb) and reached a peak hourly average concentration of 423 ppb (795 $\mu g/m^3$) at Victoria.[24] Levels of NO_2 were remarkably similar at the three London automated monitoring sites, levels close to Cromwell Road being no higher than at the other sites.

7.15 The mean black smoke level recorded by 11 stations on the 12th was 80 $\mu g/m^3$ above the monthly mean of 30 $\mu g/m^3$ but individual stations varied considerably. The highest 24-hour concentration of black smoke was 228 $\mu g/m^3$, recorded at Ilford (EC Guide Value 85-128 $\mu g/m^3$ per 24 hours, using the UK black smoke method). The highest 24-hour concentration of sulphur dioxide (SO_2) was 144 $\mu g/m^3$ (50 ppb) recorded in the City of London (EC Guide Value 100-150 $\mu g/m^3$, 37.5-56.4 ppb, per 24 hours) and, in general, levels of SO_2 did not increase to the same extent as NO_2 and black smoke. An official health warning was released and the episode received widespread publicity. London was the only city in the UK known to experience an air pollution episode at this time.

7.16 A study was commissioned by the Department of Health to investigate whether the air pollution episode in London was associated with increased mortality, hospital admissions or general practitioner (GP) consultations. Deaths from all causes, as well as deaths due to, and use of health services to treat, respiratory and cardiovascular diseases were studied.[25,26]

7.17 The method adopted was to compare mortality and hospital admissions in the episode week (beginning the 12th December) with those occurring in the previous week, and within the corresponding dates during December 1987, 1988, 1989 and 1990. The statistical technique was that of log-linear modelling; this tested the hypothesis that the risk of health events in London in the episode week differed significantly from that predicted from the control weeks and years. The mortality and hospital data were obtained from routine systems. Numbers of GP consultations for 1990-1992 were obtained from a sample of London practices covering about 300,000 patients and these were analysed in the same way.

7.18 London was also compared with three control areas: (a) the rest of England, (b) the rest of the South East, and (c) Manchester (as a similar conurbation). For the three control areas similar data sets were constructed for deaths and admissions, but these were not available for GP consultations. The analysis was then extended to include the control

areas. This tested the hypothesis that during the episode week the increased risk of illness-related events in London was relatively greater than in the control areas.

7.19 Analysis of the London data found that during the episode week, relative risks for mortality were increased for all causes (excluding accidents) (1.10; 95% confidence limits, 95% CL: 1.02, 1.19), all respiratory (1.22; 95% CL: 0.98, 1.51), respiratory infections (1.23; 95% CL: 0.89, 1.69), obstructive lung disease (chronic obstructive lung disease plus asthma) (1.23; 95% CL: 0.90, 1.68), cardiovascular disease (1.14; 95% CL: 1.01, 1.28) and ischaemic heart disease (1.18; 95% CL: 1.00, 1.39). Outer London had a higher mortality than Inner London and this was statistically significant for cardiovascular disease. When London was compared with the rest of England and the South East, the risks tended to remain increased but none was significant. More marked relative excesses emerged from the comparison with Manchester, the most notable being for all respiratory diseases (1.84; 95% CL: 1.23, 2.75) and obstructive lung disease (1.82; 95% CL: 1.03, 3.21).

7.20 Analysis of the London hospital admission data also showed increased relative risks, though less so than for mortality: all respiratory (1.04; 95% CL: 0.96, 1.13), obstructive lung disease (which included asthma) (1.14; 95% CL: 1.00, 1.30), asthma (1.08; 95% CL: 0.98, 1.28), and ischaemic heart disease (1.04; 95% CL: 0.90, 1.21). Risks were higher in the 65+ age group: all respiratory (1.19; 95% CL: 1.04, 1.37), obstructive lung disease (1.43; 95% CL: 1.15, 1.77), asthma (1.97; 95% CL: 1.10, 3.53). Compared with Outer London, admissions for respiratory diagnoses in children (0-14 years) in Inner London were higher than expected: all respiratory (1.18; 95% CL: 1.00, 1.39), asthma (1.45; 95% CL: 1.05, 1.99). When London was compared with the control areas, the relative risks tended to be reduced and lose significance, though generally remaining above 1.0. The only significant relative excess was for the comparison with the South East where an estimate of 1.55 (95% CL: 1.02, 2.37) was observed for obstructive lung disease among the 75+ age group.

7.21 General practitioner consultations in London were significantly increased for upper respiratory conditions (1.10; 95% CL: 1.03, 1.19), and were increased, but not significantly, for lower respiratory conditions (1.04; 95% CL: 0.98, 1.12), and asthma (1.14; 95% CL: 0.98, 1.34).

7.22 Broadly, the results indicated that mortality and morbidity increased during the episode, and that the greatest effect was on respiratory diseases and among older people. Only some of this excess could be explained by factors affecting the country generally at the time. Depending on the comparison area, the numbers of excess health events were estimated conservatively at between 100-180 deaths from all causes and from -30 to +90 respiratory admissions.

7.23 Various explanations for this excess mortality and morbidity were considered:

- *Chance*: The possibility that the results were obtained purely because of chance fluctuations in health events were considered unlikely because although only a few risks were significantly increased, the great majority were increased;

- *Cold weather*: Cold weather increases mortality and, possibly, hospital admissions but this seemed an unlikely explanation because it was just as cold, if not colder, elsewhere in the country;

- *Coincident epidemic of respiratory infection*: This could not be excluded, though it was known that influenza was not occurring at the time. This factor would only explain a relative excess in London if the epidemic was affecting London more than the rest of the country and other evidence suggests that this is unlikely;

- *Psychological factors*: Publicity about the health effects of the episode could affect health events by increasing utilisation or by encouraging vulnerable individuals to take steps to protect themselves. This factor would have been most likely to affect admissions or GP consultations (though it is not clear in which direction), but is

unlikely to have affected mortality;

- *Air pollution*: This was considered to be a plausible explanation but there was doubt about which component of pollution was likely to have played the most significant rôle. NO_2 reached its highest levels both historically and in relation to guideline levels and could have been responsible. Similar levels have had a small effect on lung function in two chamber studies, though not in the majority. So far, epidemiological studies have failed to establish clear evidence of an effect of NO_2 either in an episode situation or in daily time-series studies of panels or populations.

7.24 Nitrogen dioxide was not the only pollutant to increase, the other main one being black smoke, a measure of suspended particulate matter. Using daily average data from all the 11 London black smoke stations it was estimated that the average peak black smoke levels during the episode were 80 $\mu g/m^3$ above the 1991 December mean of 30 $\mu g/m^3$. Some sampling sites showed relative increases in black smoke above the seasonal mean which were just as great as the relative increase in NO_2.[26]

7.25 From meta-analyses of studies of the short term effects of particles on health,[27-29] it was possible to estimate the health effects which would be predicted with a rise of 80 $\mu g/m^3$. The predictions for all causes mortality (all ages) ranged from +3% to +8%, compared with estimates for London of from +7% to +13%, depending on the control area. For respiratory mortality (all ages), predictions ranged from +19% to +27%, compared with study estimates of from +18% to +84%. For cardiovascular mortality (all ages), predictions ranged from +8% to +11%, compared with study estimates of +8% to +15%. Finally, for respiratory admissions (all ages), predictions ranged from +4% to +6%, which compared with estimates of -1% to +6%. The predictions overlapped with the 95% confidence intervals of all of the study estimates. On the basis of these calculations it was concluded that the rise in black smoke during the episode would have been sufficient in itself to account for at least *some* of the increase in health effects. In making these predictions, it was recognised that a number of important assumptions had been made about the estimation of the relative increase in particles and equivalence of black smoke and PM_{10}; in addition, there is uncertainty in the extrapolation from studies in many differing localities to this one specific episode.

7.26 Although levels of SO_2 approached EC Guide Values, it was felt that SO_2 was unlikely to have been an important influence on the health effects. Nevertheless, it remains as a component of the mixture.

7.27 It was concluded that the air pollution episode in December 1991 was associated with an increase in mortality and morbidity and that air pollution was a plausible explanation for this increase. The mixture involved was characterised by high concentrations of NO_2, moderate concentrations of black smoke and modest levels of SO_2. It is likely that this mixture would be typical of winter pollution episodes in many other urban areas with high traffic density during conditions of still weather. Given that a single episode analysis is comparatively insensitive, statistically speaking, the observation of an effect on health in London at these levels and with this mixture suggests that smaller effects are likely to occur at lower levels of the same mixture.[25,26]

West Germany, the Ruhr 1985: SO_2 and particles

7.28 In January 1985, an episode of smog occurred in the Ruhr District of the then West Germany. The maximum 24-hour average concentration for SO_2 was 830 $\mu g/m^3$ (290 ppb), for SP (suspended particles) 600 $\mu g/m^3$, for NO_2 230 $\mu g/m^3$ (122 ppb), and for carbon monoxide (CO) 8 mg/m^3 (6.88 ppm). This episode was comprehensively investigated by Wichmann and colleagues.[30] Mortality, hospital admissions, out-patient attendances, ambulance transports and GP consultations were examined before, during and after the episode, and compared with surrounding areas of North Rhine-Westphalia. Compared with the non-polluted area, the polluted area experienced relative increases of 6% in mortality, 12% in hospital admissions, 7% for outpatients, and a relative decrease of 2% in physician contacts. There was an increase of 28% in ambulance transports but no comparable information was available from control areas. Effects were more pronounced for cardiovascular disease than for respiratory disease.

7.29 Statistical analysis indicated an effect of air pollution independent of temperature. Further analysis using data from an area with intermediate levels of pollution revealed an exposure-response gradient. Psychological factors associated with the public warnings seemed not to be a factor because the health indicator most likely to be affected by public anxiety – physician attendances – did not increase.

7.30 The report on the 1985 episode also described investigations of earlier episodes in the Ruhr District.[30] The worst was in 1962, when 24-hour concentrations of SO_2 and SP reached 5000 and 2400 $\mu g/m^3$ respectively (1750 ppb for SO_2) and were associated with a 15% increase in mortality. Other episodes in 1979 and 1982 with levels of pollution lower than those in 1985 (SO_2: 600 $\mu g/m^3$, 210 ppb; SP: 500-600 $\mu g/m^3$) appeared to have no effect on mortality.

The Netherlands, 1985: SO_2 and particles

7.31 During the 1985 episode studied by Wichmann and colleagues in the Ruhr, respiratory function measurements were being obtained on a panel of school children aged 6-11 years in an area near to Amsterdam.[31,32] During the episode, 24-hour concentrations of particles (Total Suspended Particulates, TSP and Respirable Suspended Particulates, RSP), and of SO_2 were each near 200 $\mu g/m^3$ (baseline levels in the weeks preceding and following the episode were below 70 $\mu g/m^3$). During the episode, lung function was reduced by 3-5% of the baseline value but returned to baseline in about three weeks.

The Netherlands, 1987: SO_2 and particles

7.32 This episode[33] was caused by long range transport of pollutants from the east. The highest 24-hour average concentrations of pollutants were: SO_2, 300 $\mu g/m^3$ (105 ppb); NO_2, 100 ppb (188 $\mu g/m^3$); TSP 250 $\mu g/m^3$ and black smoke, 100 $\mu g/m^3$. A group of children aged 6-12 years were monitored using lung function tests. There was a significant decline in lung function which started on the last day of the episode (on which levels of NO_2 were highest), and these deficits persisted for several weeks. The close association in time between the NO_2 peak and drop in lung function was considered unlikely to be due to NO_2 (because the levels were relatively low). Nevertheless, this is one of the few episode studies to provide information on a period of elevated NO_2 concentrations.

The Netherlands, 1991: SO_2 and particles

7.33 In February 1991, an air pollution episode occurred in which daily average SO_2 concentrations were just over 100 $\mu g/m^3$ (35 ppb), PM_{10} reached 174 $\mu g/m^3$ and the maximum 1-hour average NO_2 concentration was 127 $\mu g/m^3$ (66 ppb).[34] During the episode, measures of lung function (FVC, FEV_1 and maximum mid-expiratory flow, MMEF) were slightly lower than on baseline days in a panel of 112 children aged 7-12 years, but no effects on symptoms were observed. Unlike the 1991 London episode, the levels of NO_2 were quite low; however the increases in SO_2 and particles were similar to those observed in parts of London during the 1991 episode.

New York City, USA: SO_2 and particles

7.34 During the 1950s and 1960s, New York experienced a number of air pollution episodes which were characterised by increases in SO_2 and particles (measured as smoke shade).[35-38] An episode in 1953 was associated with an approximately four-fold increase in daily smoke shade levels to 8.38.[35,36] Sulphur dioxide concentrations, measured as total acidity, increased from the average range of 150-200 ppb (430-570 $\mu g/m^3$) to a maximum value of 860 ppb (2460 $\mu g/m^3$). There was an increase in mortality and clinic visits for upper respiratory illnesses and "cardiac visits" in all four hospitals studied but no increase in the number of visits for asthma.

7.35 In 1966 another episode occurred during which maximum hourly concentrations of SO_2 increased to 1000 ppb (2860 $\mu g/m^3$) from the more usual maximum values of about 400 ppb (1140 $\mu g/m^3$), and the daily mean of hourly concentrations from 170 to 520 ppb (486 to 1490 $\mu g/m^3$).[37] The daily mean of 2-hour smoke shade increased from about 3.0 to 6.0. The temperature was unusually *warm*, being 13°F (7.2°C) higher than average. An increase in mortality was detected, amounting to 24 deaths per day and 168 deaths altogether. There was an increase in emergency visits for bronchitis and asthma in those over 45 years of age but the concurrence of Thanksgiving Day makes utilisation data difficult to interpret. Other workers obtained questionnaire data from a sample of white collar workers and reported evidence of an increase in upper and lower respiratory symptoms which was greater in those with existing respiratory problems.[38]

Steubenville, USA 1978-79: SO_2 and particles

7.36 Lung function (FVC and $FEV_{0.75}$) was measured in school children before and after two air pollution alerts in 1978 and 1979 when TSP concentrations exceeded the US 24-hour standard (260 $\mu g/m^3$).[39] In 1978, TSP levels reached 422 $\mu g/m^3$ and SO_2 281 $\mu g/m^3$ (98 ppb). In 1979, TSP reached 271 $\mu g/m^3$ and SO_2 455 $\mu g/m^3$ (159 ppb). Following both alerts, forced vital capacity (FVC) fell significantly by about 2%, and forced expiratory volume ($FEV_{0.75}$) fell by 4% after the 1979 alert.

7.37 A summary of studies of various episodes, the results, and an assessment of the likelihood of the observed conditions occurring in the UK is given in Annex 7A.

Studies of daily variations in health events – panel studies

7.38 Studies of daily variation in health indicators have the potential to control for possible confounders and to separate the effects of different pollutants. This is because multiple rather than single days are analysed and the various factors which might influence health rarely co-vary completely. There are two main types of daily time-series study.[40] One is the so-called panel study in which individuals (healthy or with pre-existing respiratory disease) are followed day by day with measurements of symptoms, lung function, or medication use. These have the advantage of analysing the data at an individual level. The other main form of daily time-series study uses population or aggregated data for each day, usually mortality or hospital admissions. Unlike panel studies, the data can only be analysed at the group level.

7.39 In panel studies, the usual statistical approach is to analyse the data (usually lung function, but symptoms and medication use may also be available) for each individual separately using regression techniques which allow for serial correlation (the tendency for variables on one day to be correlated with those on the next or subsequent days). The analysis is controlled for confounding factors such as weather variables and provides a coefficient which relates lung function to levels of pollution. Grouping of the individual results is done by using weighted means or by other methods. In such studies, exposure to pollution is usually measured at nearby monitoring sites and the level of physical activity (which affects ventilation) may also be recorded.

7.40 The results of panel studies of the effects of ambient pollution have been described and summarised in the previous reports.[1-3] Studies which have been published since then are summarised in Annex 7B. The newer studies serve to consolidate rather than change the earlier conclusions. Fortunately, there are now more reports from Europe, including several from the UK (some in abstract form at present).

Summer pollution characterised by increased ozone levels

7.41 A considerable number of panel studies have examined the relationship between summer-type pollution and health related effects. Some have been carried out in rural or mountain areas where the levels of other pollutants are low. Others have taken place in urban or suburban areas where other pollutants have been present, especially NO_2 but also particles. The majority have studied healthy children but in some instances asthmatic children or adults with obstructive lung diseases, including asthma have been studied.

7.42 A number of conclusions emerge from these studies:

- The majority of studies have found significant relationships between increased O_3 and reduced lung function. The defect is mainly restrictive with an element of obstruction.

- The mean effect is small, amounting to a decrease of about 3% in the FEV_1 and vital capacity in a child over the usual range of exposure, but there is considerable individual variation with some subjects showing much larger reductions. Asthmatics are not unduly sensitive.

- Associations have been observed at levels of O_3 as low as 80 ppb (160 $\mu g/m^3$, hourly average), a level regularly exceeded in the south of England.

- The effects on ventilatory function are greater than would be predicted from exposure chamber studies. This is an important observation because it might

indicate that the pollution mixture of which O_3 is a part is more toxic than O_3 itself. Alternatively, there may be important differences between chamber and ambient exposures which affect the dose received by the lung.

- In normal subjects when symptoms have been sought none have generally been observed.

- There is some indication that exacerbation of symptoms in asthmatics may be more likely to occur in urban situations where the pollution mixture is likely to be more complex than in situations where the main pollutant is O_3. One large study of asthmatic young adults in Los Angeles found an association between attacks and high pollution days characterised by oxidants, NO_2, and particles.[41] More recent evidence from Mexico City suggests that school absence is associated with increased O_3 levels, possibly interacting with low temperatures.[42] On the other hand, summer camp studies in North America (where O_3 is the main pollutant) have not found associations between O_3 and symptoms in asthmatic children. Those studies showing effects on symptoms have tended to be in regions where O_3 levels are higher than are likely in southern England.

European studies

7.43 Recent European studies from The Netherlands[43] and Switzerland[44] have reported an effect of O_3-related pollution on lung function in children, see Annex 7B. In the Dutch study, children with chronic respiratory symptoms were not found to be affected more than healthy children. In the Swiss study, the slope of the relationship between O_3 and lung function was steeper in the area (Chiasso) with greater background levels of NO_2, though this was not statistically significant. This would be consistent with an interactive or additive relationship between the two pollutants. One study from the northwest of England found that in August and September daily concentrations of O_3 and SO_2 were associated with reductions in lung function of adults, more so in those with bronchial hyperresponsiveness (assessed with methacholine).[45] However, these findings must be viewed with caution since there was no allowance for autocorrelation (which could produce spurious findings), and the effects of covariation of pollutants were not explored.

Particles and sulphur dioxide

7.44 Winter episodes characterised by increased SO_2 and particles emitted by coal combustion are now uncommon in the UK with the exception of Belfast and some coal-mining areas of Yorkshire. The more general relevance of this form of pollution to acute health effects now depends on the extent to which the effects of pollution are generic or specific. Panels of chronic bronchitics (without asthma) studied in London in the 1960s showed relationships between pollution and symptoms when daily black smoke levels exceeded about 250 $\mu g/m^3$ and 24-hour average SO_2 concentrations exceeded 500 $\mu g/m^3$ (175 ppb).[19]

7.45 Using measures of lung function, similar conclusions have been reached in studies in the US and in Europe,[31,33,39,46] with small reductions being observed when daily average SO_2 concentrations reach 100 ppb (286 $\mu g/m^3$) and rather greater reductions of 5-7% when 24-hour average SO_2 concentrations reach 189 ppb (540 $\mu g/m^3$) (see paragraphs 7.19 and 7.20 of reference 2).

7.46 Recent reports from The Netherlands[47,48] have described relationships between increased levels of particles and SO_2 and reductions in lung function in healthy children and an increase in symptoms and use of medications among children with pre-existing respiratory disease. The pollution levels are quantitatively and qualitatively similar to those which occur in the UK (with perhaps a greater contribution from SO_2) and are well within current guidelines.

7.47 In one study from northwest England,[49] it was reported that during winter months a panel of adult asthmatics with bronchial hyperresponsiveness showed greater daily variability of lung function in relation to SO_2 but not to NO_2. The published report is awaited.

Nitrogen dioxide and particles (due to motor vehicle emissions)

7.48 The previous report on the oxides of nitrogen described in detail several panel studies which are relevant to the UK at the present time.[3] In particular, two European studies, one from Oslo[50] and the other from Switzerland[51] were of interest because the source of emissions (traffic) and the ambient concentrations were very similar to those in parts of the UK. Both reported short term effects at levels lower than then current guidelines. The study from Basel and Zurich investigated children during a 6 week period during which average concentrations of NO_2 ranged from 13-28 ppb (passive samplers), and of TSP from 30-117 $\mu g/m^3$. A significant relationship between TSP and upper respiratory symptoms was found. The duration of respiratory symptoms was increased in association with both NO_2 and TSP but, in statistical terms, the association with TSP was more convincing.[51]

7.49 The pollution mixture in Oslo was similar to that in urban areas of the UK with maximum hourly average concentrations of NO_2 reaching 140 ppb (263 $\mu g/m^3$; three month average 30-34 ppb, 56-64 $\mu g/m^3$), and the maximum hourly average of PM_{10} reaching 156 $\mu g/m^3$. Diary studies in adults showed significant relationships between NO_2 (used as an indicator for traffic pollution) and various upper and lower chest symptoms, but not with ventilatory function.[50]

7.50 Two recent European studies, one among adult asthmatics in Denmark[52] and the other in healthy German children[53] have both reported an inverse association between NO_2 and lung function. The nature of the whole mixture to which these panels was exposed is not clear but the Danish panel were also exposed to SO_2.

Time-series studies using aggregated population data

7.51 Many studies of this type have been reported, but few have appeared from the UK in recent years, apart from American analyses of historic London data. These studies utilise routinely collected or available data on mortality, morbidity or health service utilisation. They effectively control for "stable" confounders such as social class, smoking, occupational exposure *etc.*, because these do not change from day to day. On the other hand they are prone to confounding by temporal factors which may be related to both air pollution and health effects, the chief ones being seasonal factors, weather and respiratory infection epidemics – influenza in particular.

7.52 The currently accepted statistical technique is to model the data so that the effects of secular trends, long and medium term cycles (usually down to one month), temperature and other meteorological variables, day of the week, holidays and known influenza epidemics are removed. Various transformations and lags of the pollutant data may be tried. These may be based on *a priori* hypotheses or simply tested until the best fit for the model is obtained. The effects of air pollutants are then examined using regression analysis (including allowance for serial correlation because health events on one day may be associated with health events on previous days). When the number of daily events is small, Poisson regression is usually employed. From such analyses values are obtained which describe the relative risk due to, or the proportional effect of, an increment of pollution. For example, the effect of a 10 $\mu g/m^3$ increase in, say, PM_{10} might be to increase mortality in proportional terms by 1% within the range studied. Co-variation of pollutants is common, but, by putting more than one pollutant into the model, the independent effects of different pollutants may be examined; this technique does not lend itself to the investigation of mixtures. Because large populations are usually necessary for such studies, the measurement of ambient exposure is imprecise and this can lead to bias in either direction.[54] Also, the actual dose received will depend on other factors, such as the time spent indoors, the level of ventilation and exposures to other pollutants.

7.53 A considerable number of studies using acceptable methodology have now been reported, mainly from the USA and Canada but increasingly from Europe. Many have been reviewed in previous reports[1-3] and more recent ones are listed in Annex 7C. As is the case for other types of study, their relevance to the provision of medical advice during episodes depends on the degree to which the pollution is likely to resemble the mixtures which occur in the UK, the level of pollution and the exposure-response relationship. Many time-series studies comprise a number of years of consecutive data and the effects may be obscured if there are any seasonal differences in the pollution mixture. Some

analyses take this into account by analysing winters or summers separately or by including an interaction term for season.

7.54 An important issue for this report is the fact that the effects of pollution are usually analysed pollutant-by-pollutant and not in terms of the existing mixture or some index of that mixture. In addition, the pollutants examined normally reflect those which happened to be available to the study, *i.e.* had been monitored adequately. Some studies address this by examining the independent effects of various pollutants and the existence of interactions, if any. The strength of an association, and its persistence after controlling for other pollutants, are among the criteria for concluding that, in the mixture, one pollutant rather than another is responsible for the health effects. This is the basis for many North American studies which have concluded that particles rather than gaseous components are important. Due to the statistical complexities of these analyses and the small effects involved, few if any analyses have successfully disentangled the separate or joint effects of all the main pollutants which comprise the prevailing mixture.

Particles and sulphur dioxide

7.55 Some of the points in the previous paragraph are well illustrated by the extensive literature which exists on daily mortality for London from 1958 to 1972. For this period, daily levels of black smoke, SO_2 and aerosol acid are available and various American workers have examined the association between these and daily mortality. It is notable that the results of these analyses have varied considerably with respect to the apparent importance of the various pollutants. Whilst all have found associations between daily mortality and black smoke, there have been different findings in respect of the rôle of SO_2; these probably reflect differences in the methodology of analysing variables which tend to co-vary quite closely.[55-57] Similarly, the findings concerning the relative rôle of acid aerosols has also varied.[58,59] In a recent paper which reviewed previous studies,[60] a different approach was employed in which analyses were carried out within narrow bands of temperature, thus removing the effect of temperature from the analysis. It was found that there were strong associations between daily mortality and daily acid and SO_2 while the associations with black smoke were weaker. Thus, for London during that period, it seems that attempts to isolate the most important pollutant by statistical means have not yielded consistent results and that it is safe to conclude only that the mixture itself was almost certainly toxic. The levels in London at that time were higher than would occur in the UK today.

7.56 Associations with health effects have been reported in areas such as the West Midlands, where SO_2 levels are moderately high;[61] effects would, therefore, also be expected in areas such as Belfast, where the highest UK levels are recorded. Where the relative effects of SO_2 and particulate components have been examined the results are conflicting. There is a tendency for particles to appear to be more important, although some studies, in France for example, have found that the effects of SO_2 are dominant.

7.57 In the West Midlands study, Walters *et al.*, in an analysis of the Birmingham hospital admission data for asthma in the years 1989-90, found positive associations with SO_2 during winter periods.[61] The occurrence of an influenza epidemic in one of the winters studied clouds the interpretation of these results. It is likely that the mixture included particles and NO_2.

Particles alone

7.58 The health effects of inhalable particles are currently being reviewed by the Department of Health's Committee on the Medical Effects of Air Pollutants and will not be discussed in detail here. A report is currently in press.[8] Sources of particles include coal combustion, industrial processes and motor vehicles (especially those with diesel engines). With rare exceptions, gaseous pollutants will accompany the particulate pollution. There are different methods of measuring particles and there is no sure and simple way of converting different measures to equivalent units. In some respects it is useful to consider the particle fraction as a mixture of its own, varying in the distribution of particle size and in chemical composition. It is known that the nature of particles is likely to differ in different places and, in any one place, to vary at different times and seasons. This makes it difficult to generalize from overseas studies to the UK, or even within the UK. The associated gaseous pollutants, whilst easier to measure, also show differing patterns.

7.59 Exposure to particles alone will not occur in the UK given the usual types of emissions with which they are associated. However, a number of time-series studies report only particle concentrations and most recent reviews and meta-analyses have been confined to their effects.[27-29] The evidence suggests that a large variety of health effects (mortality, admissions, emergency room visits, absenteeism from work and school, primary care use) are associated with levels of particles such as may be observed currently in the UK. These associations have been identified in a wide variety of environments, in both winter and summer, and with varying sources of particles. Studies from Utah where the particulate exposure (from an industrial source) is largely unaccompanied by gaseous pollution suggest that particles alone may be associated with health effects.[62] However, these particles may be very different chemically from those typical of UK urban areas.

7.60 Available meta-analyses of the time-series studies make various assumptions concerning the equivalence of different measures of particles (black smoke, TSP, PM_{10}); these are largely unvalidated. Unpublished data from the National Environmental Technology Centre on co-located PM_{10} and black smoke monitors indicate that, in London, the relationship between the two may not be that which obtains elsewhere or has been assumed in the meta-analyses. It would be very difficult for such meta-analyses to take gaseous pollutants into account but, nevertheless, their omission leads to difficulties in assessing the effects of the mixtures for which particles may be the only indicator, since the gaseous mix is likely to vary from place to place. In spite of this, the consistency of the relationships between particles and health effects is remarkable. This raises the question of whether particles have a generic effect irrespective of their origin. If so, extrapolation to the UK situation would be more reliable.

Particles and NO_2

7.61 This combination is typical of the winter situation in many towns in the UK but there are few time-series studies which are directly relevant. One, from Helsinki (where raised levels of particles are partly due to gritted roads and the use of studded tyres), found that admissions for asthma were increased when NO_2 and TSP were increased. The levels were low, the 75th percentiles of NO_2 and TSP being 46 $\mu g/m^3$ (24 ppb) and 93 $\mu g/m^3$, respectively.[63]

7.62 A study from five towns in the former West Germany found that daily consultations for croup in children were associated with TSP and NO_2 concentrations (but not with SO_2). Levels were low in comparison with WHO guidelines, with the 90th percentile for daily average NO_2 concentrations ranging from 18 to 45 ppb (34 to 85 $\mu g/m^3$). Of relevance to the UK is the fact that it was not possible to separate the effects of TSP and NO_2; thus it may be concluded that this mixture may be associated with croup at low levels.[64]

Particles and ozone

7.63 Ozone levels increase during the summer in the UK, depending on the weather and availability of precursors. Levels of NO_2, and possibly particles, may be raised moderately (up to WHO guideline levels). Relevant studies therefore include those in which these pollutants were present at moderate levels (raised, but below WHO guideline levels).

7.64 North American studies tend to indicate that acid summer haze (comprising a mixture of O_3, NO_2, sulphates, nitrates and other pollutants) may be associated with increased hospital admissions for respiratory disease, though some studies have found no relationship and, at least one, a negative relationship with O_3. Since the publication of this group's 'Ozone' report,[1] a number of additional studies from California have been reported which confirm a relationship between O_3 and adverse health effects, including mortality.[65-67] Ozone levels there tend to be higher than in the south east of England but, if a relationship exists at lower levels, as seems to be likely, these results are clearly relevant to the UK.

Causal inference in time-series studies

7.65 At this point it is important to draw attention to the arguments concerning the causal nature of the associations observed in time-series studies at low levels of pollution. The effects are, on the whole, small and there are various potential confounding influences which might not be adequately removed by the analytic techniques employed. In addition, there is the question of biological plausibility. The strongest argument for causality is the

consistency of the findings of many studies carried out in many different environments and in different seasons. Of course, there might be something consistently wrong with the analyses or some confounder might be inextricably associated with pollution, but none has been suggested which is more plausible than pollution itself.

7.66 It should, however, be recognised that there are several processes which could lead to consistency of results through a process of bias. Many of the analyses do not state an *a priori* hypothesis as to the responsible pollutant, its lag effect or dose-response. Different possibilities may be tried and only those which emerge as significant or interesting may survive to be published. The selective publishing of positive findings could be very important but its extent is unknown.

7.67 The biological plausibility of an air pollution effect on mortality and other health outcomes is an important, though not essential, strand in the argument concerning the causal nature of these associations. This has been addressed in a number of reviews.[68-70] At first sight, it might seem unlikely that a small increase in air pollution would be capable of increasing serious events such as mortality. This is because there is a tendency to think of the toxicity of air pollutants in terms of their effects on healthy subjects. In reality, populations comprise a mixture of healthy and diseased persons and some of the latter will be close to death or some other health event. For some of these the added effect of air pollution is the "last straw". We know that ambient levels of pollution have measurable pathological and physiological short term effects on healthy and asthmatic children and adults. Such effects in a person with severely compromised cardiorespiratory function could be sufficient to have a deleterious effect. Further, most studies tend to confirm that the effects are greatest in patients with respiratory disease, followed by those with cardiovascular disease – as would be predicted if this were the pathophysiological mechanism. A consequence of this argument is that some of the additional deaths will have occurred amongst persons who would have died soon anyway; the extent to which such short term "harvesting" occurs is not well known.

Conclusions

7.68 The epidemiology of the health effects of mixtures of air pollutants is poorly developed. Pollutants tend to be analysed separately and some pollutants are either not measured at all or are poorly characterised (especially particles). Thus, we have an incomplete picture of the pattern of exposure in reported studies of health effects. This is in addition to the other well-known problems associated with ascertaining the actual exposure of the population under study, and the dose received by the lung.

7.69 Even where the pattern of exposure is reasonably well described, the analysis tends to be in terms of individual pollutants rather than of mixtures; so far, little progress has been made in developing accepted indices of mixed pollution exposure.

7.70 In the absence of enough local research from the UK, it has been necessary to extrapolate from studies elsewhere. Most confidence has been placed on recent studies where the emission sources and weather conditions are somewhat similar, Europe in particular. If pollutants were to have generic effects, as has been suggested for particles, extrapolation would be possible to a greater extent. This is not unreasonable since the lung has a limited repertoire of responses to particles and toxic gases.

7.71 Three types of research design are available for examining short term effects and all have methodological weaknesses which must be considered when examining the evidence for a statistical association and casual relationship.

7.72 Episode studies are essentially one-event analyses and are subject to low statistical power, confounding and coincidental influences. As the investigation of the 1991 episode illustrates, important effects are difficult to demonstrate, even in a large city such as London. Nevertheless, the design of episode studies is easy to understand and their results are directly relevant to policy concerning standards and medical advice during episodes.

7.73 The evidence from episode studies is reasonably convincing that air pollution may cause adverse health effects. More importantly, the studies of lung function in children

from The Netherlands, of asthmatics from Birmingham and of the population of London during the 1991 episode, all indicate that adverse health effects may occur in the winter pollution conditions which can arise in the UK. If health effects do occur during episodes, the most noticeable are likely to involve those subjects (mainly older) with advanced cardiorespiratory disease. There are no published studies of the effects of single summer O_3 episodes in the UK, but unpublished data relating to the 1976 episode indicate that hospital admissions and mortality increased at the time. While consistent with an effect of O_3, high temperatures could also have been responsible.

7.74 The results of panel studies are particularly important for investigating the effects of air pollution on lung function and, in subjects with pre-existing disease, the exacerbation of symptoms or increased need for treatment. From published evidence, it is likely that all the three main types of pollution mixtures encountered in the UK are likely to cause small mean reductions in lung function during episodes. The evidence for this is probably strongest for O_3-related pollution. In healthy subjects, symptoms are unlikely and there is no clear evidence that asthmatics are especially susceptible. Individual variability occurs however, and subjects' respiratory conditions might become symptomatic, or if already symptomatic, worse than before.

7.75 Time-series studies using aggregated data also suggest that health effects may be associated with levels of pollution which exist in the UK. The evidence is best for particles, which are a component of both NO_2- and SO_2-associated winter pollution and which will also be present during still weather in summer. Ozone-related pollution may also be important. While there is some evidence that low levels of particles alone may have health effects, there is less certainty about the effects of NO_2 and SO_2 alone and at low levels. Little is known about the interactions, if any, between the various pollutants.

7.76 Taking all of the evidence for acute effects together, it is concluded that episodes of air pollution (as discussed in Chapter 3) which now occur in the UK from time to time, whether characterised by O_3, NO_2, SO_2 or particles may have small acute effects on lung function in healthy subjects and may cause a worsening of the condition of people with existing cardiorespiratory disease. Effects could also be occurring at levels of pollution below those experienced in air pollution episodes.

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Studies of public health effects of air pollution episodes

Reference	Place and date	Exposure	Health effects	Relevance to current or future United Kingdom conditions
Ministry of Health 1954[14]	London 1952	Average daily Total Suspended Matter up to 1.6 mg/m^3 (5 × usual level). SO_2 up to 1340 ppb. Acidic particles probably increased	Mortality increased 2.3×, hospital admissions 1.5-2.5 ×. Increase in GP consultations for upper and lower respiratory disease in older patients	Mixture and scale of episode is unlikely to re-occur
Martin 1960[16]	London 1958-1959	Multiple episodes	Increase in mortality with increases in black smoke and SO_2 above 1000 µg/m^3 and 250 ppb, respectively	Mixture is unlikely to re-occur, but scale of relative increase in particles is possible
Lawther *et al.* 1970[19]	London 1950s and 1960s	Smoke and SO_2, different conditions. Acid also present	Increases in air pollution associated with increased symptoms in panels of chronic bronchitics. Not observable at levels below 500 µg/m^3 SO_2 or 250 µg/m^3 black smoke. Unpublished observations that lung function was affected in some subjects	Mixture is different from the current one. Levels higher. Results may not apply to asthmatics
Anderson *et al.* 1995 [25,26]	London 1991	Maximum hourly NO_2: 423 ppb, Average black smoke (11 sites) 148 µg/m^3 (highest 228 µg/m^3), maximum hourly SO_2: 144 µg/m^3. Episode lasted 4 days	Increase in mortality and hospital admissions for respiratory and cardiovascular diseases. Increase in GP consultations for upper and lower respiratory disease	Current UK situation. Could occur again
Walters *et al.* 1993[23]	Birmingham 1992	Maximum hourly NO_2: 207 ppb, maximum hourly SO_2: 130 ppb, maximum hourly PM_{10}: 231 µg/m^3	Reductions in lung function and increase in medications observed in severe (brittle) but not milder asthmatics	Current UK study
Dassen *et al.* 1986[31]	The Netherlands 1985	Daily TSP and SO_2 200-250 µg/m^3 (base-line about 100 µg/m^3)	Reduction in lung function by 3-5% in children. Back to normal in 3 weeks	Mixture could be relevant to Belfast. Particle levels could occur in UK
Brunekreef *et al.* 1989[33]	The Netherlands 1987	Maximum 24-hour SO_2: 300 µg/m^3, maximum 24-hour NO_2: 100 ppb, maximum 24-hour black smoke: 100 µg/m^3, maximum 24-hour TSP: 250 µg/m^3	Decline in lung function of children which persisted for several weeks	Relevant to UK
Hoek and Brunekreef 1993[34]	The Netherlands 1991	Maximum 24-hour SO_2: 100 µg/m^3, maximum 24-hour PM_{10}: 174 µg/m^3; maximum 24-hour NO_2: 66 ppb	Significant reduction in lung function but no effect on symptoms	Relevant to UK

Annex 7A (continued)

Studies of public health effects of air pollution episodes

Reference	Place and date	Exposure	Health effects	Relevance to current or future United Kingdom conditions
Wichmann *et al.* 1989[30]	Ruhr, Germany 1985	Maximum 24-hour SO_2: 830 µg/m^3, maximum 24-hour SP: 600 µg/m^3, maximum 24-hour NO_2: 230 µg/m^3	Increased mortality, hospital admissions, out-patients and ambulance transports. No change in physician contacts	Levels are not likely to occur in UK
Dockery *et al.* 1982[29]	Steubenville, USA 1978-1979	Two episodes: maximum 24-hour TSP: 422 and 271 µg/m^3, maximum 24-hour SO_2: 281 and 455 µg/m^3	Reduction in lung function occurred during both episodes. $FEV_{0.75}$ by 2% and FVC by 4%	Higher than likely in UK
Greenburg *et al.* 1962[35]	New York, 1953	About 3-fold increase in particles (smoke shade) and SO_2	Increase in mortality and clinic visits for upper respiratory and cardiac illnesses but not in asthma visits	Mixture and scale likely to be different to UK
Glasser *et al.* 1967[37], Becker *et al.* 1968[38]	New York, 1966	Hourly maximum SO_2: 1000 ppb; Smoke shade up to 6.0	Increase in mortality and emergency visits for bronchitis and asthma in persons over the age of 45	Mixture and scale unlikely to occur in UK

Recent panel studies of public health effects of air pollutants

Reference	Place	Exposure	Health effects	Relevance to current or future United Kingdom conditions
Ozone-related (with or without NO_2 or particles)				
Hoek *et al.* 1993[71]	The Netherlands	Highest level 236 µg/m^3	Exercising children. Small reduction in PEFR associated with previous day's maximum O_3 level. Effect of same day's O_3 could not be separated from that of temperature	Summer O_3-type pollution. Similar levels in UK
Hoek *et al.* 1993[43]	The Netherlands 1989	Episodes above 160 µg/m^3 but below 240 µg/m^3	Children at rest in three different areas. Significant negative associations between lung function and previous day's 1-hour maximum O_3 level. Children with chronic respiratory symptoms not affected more than healthy children	Summer O_3-type pollution. Similar levels in UK
Ostro *et al.* 1993[67]	California 1978-9	O_3 1-hour daily maximum: mean 98.6, range 20-430 ppb. Coefficient of haze (per 100 feet): mean 11.55, range 4.04-26.45	Adult non-smokers. Increased incidence of lower respiratory tract symptoms and 1-hour daily maximum O_3 levels (odds ratio of 1.22 for change of 100 ppb), but no association with index of particles. Greater effect in those with pre-existing respiratory infection	Summer O_3-type pollution. Levels rather higher than in UK
Higgins *et al.* 1995[45]	England, August and September 1991	Maximum 24-hour average for: O_3 - 55 µg/m^3; SO_2 - 117 µg/m^3; NO_2 - 84 µg/m^3	Adults with chronic bronchitis or asthma recruited from general practice, classified by BHR into reactors and non-reactors. SO_2 and O_3 had significant effect on respiratory function especially those with BHR	Summer O_3 type pollution especially where there is also SO_2. UK study
Braun-Fährlander *et al.* 1994[44]	Southern Switzerland during summer	Two areas with similar levels of O_3 (30 min means 40-157 µg/m^3). Differences in NO_2 (means 70 µg/m^3 and 18 µg/m^3)	Children exercised for 10 minutes on cycle ergometer. Pre-post exercise differences in ventilatory capacity inversely related to O_3. Larger slopes in Chiasso (with more NO_2), but this was not significant	Summer type pollution. Hint of enhanced response to O_3 in presence of higher levels of NO_2

Recent panel studies of public health effects of air pollutants

Reference	Place	Exposure	Health effects	Relevance to current or future United Kingdom conditions
NO_2-related (with particles)				
Moseholm *et al.* 1993[52]	Denmark	SO_2 and NO_2 at low levels	27 non-allergic adult asthmatics. Inverse relationship between SO_2 and NO_2 and PEFR at levels above 40 µg/m^3	NO_2 or SO_2 associated pollution. Levels probably comparable to UK
Frischer *et al.* 1993[53]	Austria, 2 surveys in period of January-June 1990	NO_2 levels below current Austrian air-quality standards. Mean 24-hour average ranged from 9.7 to 32.2 µg/m^3	Changes in lung function in children between two surveys over a 6-month period. Decrease in NO_2 between surveys significantly associated with increased FVC. Increase of 1.5 ml in FVC for decrease of 1 µg/m^3 NO_2 (in terms of the 2-hour mean preceding lung function measurement)	Unusual design. Confounding may be present. Otherwise very relevant to UK. Other pollutants may have been present
SO_2-related (with particles)				
Hoek *et al.* 1992[47]	The Netherlands, winter 1990-91	SO_2, NO_2, BS, PM_{10} Highest 24-hour average PM_{10} was 174 µg/m^3	Unselected children and panel of children with chronic respiratory symptoms. In both groups significant but small inverse association between lung function and particles and SO_2, but not NO_2. In panel there was a positive association between prevalence of wheeze and bronchodilator use with particles and SO_2 but not NO_2. Particles and SO_2 highly intercorrelated	Winter pollution with particles, SO_2 and NO_2. Similar levels to UK
Roemer *et al.* 1993[48]	The Netherlands, winter 1990-91	Maximum 24-hour PM_{10} 110 µg/m^3, maximum 24-hour SO_2 105 µg/m^3, maximum 24-hour NO_2 127 ppb	Children with respiratory symptoms at rest. Small but consistent negative associations between PM_{10}, BS and SO_2 and lung function. Consistent positive association with these pollutants and prevalence of wheeze and bronchodilator use	Winter type pollution at levels commonly encountered in UK. SO_2 may be a greater feature of mixture than in most UK areas
Taggart *et al.* 1994[49]	Northwest England	Mean 24-hour levels below WHO Guidelines. Maximum 24-hour SO_2 169 µg/m^3, maximum 24-hour NO_2 151 µg/m^3	20 adult reactors to methacholine showed significantly greater variability (amplitude as % mean) with increased SO_2 lag 1 day. Effect on mean PEFR was borderline significance. No association with NO_2. No comment about non-reactors, assume that no effect observed	UK study. Relevant to winter pollution in UK

Time-series studies of the health effects of air pollution

Reference	Place of study (type of study)	Pollutant (unit of measurement) type of measurement	Categorisation of exposure	Health effects studied	Results	Relevance to current or future United Kingdom conditions
Katsouyanni *et al.* 1993[72]	Athens (population study)	O_3, SO_2 and smoke (all µg/m^3) maximum 1-hour values	Daily mean above or below 150, 80, 125, respectively	Daily mortality. Mortality data was not cause-specific	Significant interaction effect of temperature >30°C and SO_2 >80 µg/m^3 on mortality. With smoke and O_3 only, $P < 0.20$	Pollutant levels generally higher than in the UK
Schwartz 1994[73]	Birmingham, Alabama (population study)	O_3 (ppb) daily average	Mean: 25 10%ile: 14 90%ile: 37	Hospital admission data for persons aged 65 or over with discharge diagnosis of COPD or pneumonia	Ozone, with 1 or 2 day lag, was a non-significant risk factor. PM_{10} (100 µg/m^3 increase) was a significant risk factor for pneumonia (RR 1.19, 95% CL 1.07-1.32) or COPD (RR 1.27, 95% CL 1.08-1.50)	Possibility of equivalent values being reached in the UK
		PM_{10} (µg/m^3) daily average	Mean: 45 10%ile: 19 90%ile: 77			
Schwartz *et al.* 1993[74]	Seattle (population study)	PM_{10} (µg/m^3) daily average	Mean: 29.6 minimum: 6 maximum: 103	Emergency room visits for asthma of persons under 65 to 8 hospitals	With SO_2 there was no significant association. PM_{10} exposure on the previous day, and, better, the mean of previous 4 days' PM_{10}, were significant predictors of asthma visits	PM_{10} values are comparable with those in UK. PM_{10} composition differences not known
		SO_2 (pbb) not specified	Mean: 6.5 minimum: 0 maximum: 29			
Lippmann and Ito 1995[60]	London 1965-1972 (population study)	Aerosol acid (µg/m^3 as H_2SO_4) daily average	Data plotted, no tabulated figures	Daily mortality in Greater London. Data analysed by season	Strong associations of acidity and SO_2 with daily mortality; not confounded by seasonal variations. Weaker association of black smoke with mortality	Historic London conditions, not likely to re-occur
		SO_2 (µg/m^3) daily average	Data plotted, no tabulated figures			
		black smoke (µg/m^3) daily average	Data plotted, no tabulated figures			
Burnett *et al.* 1994[75]	Ontario, Canada 1983-1988 (population study)	O_3 (ppb) daily 1-hour maximum	Many sites, range of summer means: 32-70	Daily emergency or urgent respiratory admissions to 168 acute care hospitals	Significant positive associations between admissions and both O_3 and sulphates on day of admission or up to 3 days beforehand	Ozone levels may occasionally be reached in the UK
		Sulphates (µg/m^3) daily average	Many sites, range of summer means: 3.1-8.2			

Annex 7C (continued)

Time-series studies of the health effects of air pollution

Reference	Place of study (type of study)	Pollutant (unit of measurement) type of measurement	Categorisation of exposure	Health effects studied	Results	Relevance to current or future United Kingdom conditions
Schwartz 1994[76]	Detroit (population study)	PM_{10} ($\mu g/m^3$) 24-hour mean	Mean: 48 10%ile: 22 90%ile: 82	Daily hospital admission data of persons aged over 65 years for pneumonia, COPD and asthma versus all other COPD	Association of both O_3 and PM_{10} with admissions for both pneumonia and COPD other than asthma. No association of asthma admissions with either pollutant	Ozone and PM_{10} values are comparable with those in UK. PM_{10} composition differences not known
		O_3 (ppb) daily mean of 1 hour readings	Mean: 21 10%ile: 7 90%ile: 36			
Schwartz 1994[34]	Minneapolis – St Paul 1986-1989 (population study)	PM_{10} ($\mu g/m^3$) mean 24-hour samples from all sites	Mean: 36 10%ile: 18 90%ile: 58	Daily hospital admission data of persons aged over 65 years for pneumonia, and COPD	PM_{10} was a risk factor for both pneumonia and COPD admissions. O_3 was also associated with pneumonia admissions	Ozone and PM_{10} values are comparable with those in UK. PM_{10} composition differences not known
		O_3 (ppb) daily mean of 1-hour readings; all sites averaged	Mean: 26 10%ile: 11 90%ile: 41			
Thurston *et al.* 1994[77]	Toronto 1986-1988 (population study)	O_3 (ppb) daytime maximum 1-hour value	Range of annual mean and maximum: 49-70 and 86-159	Daily counts of a) total respiratory admissions, b) asthma admissions, and c) nonrespiratory control admissions to 22 acute care hospitals	Ozone, particulate acidity and sulphates were significantly and consistently associated with total respiratory and asthma admissions. On peak pollution days particulate acidity provided the highest relative risk estimates	Ozone and PM_{10} values could be reached in the UK
		PM_{10} ($\mu g/m^3$) 24-hour average	Range of annual mean and maximum: 29-39 and 80-96			
		Sulphates (nmole/m^3) daytime	Range of annual mean and maximum: 38-124 and 241-508			
		Particulate acidity (nmole H^+/m^3) daytime	Range of annual mean and maximum: 13-52 and 67-391			

Abbreviations: TSP, total suspended particulates; 10%ile, value below which 10% of the measurements fall; 90%ile, value below which 90% of the measurements fall; COPD, chronic obstructive pulmonary disease; RR, relative risk.

Chapter 8

Summary, Discussion and Recommendations

8.1 This chapter summarises the main conclusions that arise from the individual chapters in the report before discussing the main recommendations. In the United Kingdom, as in other countries, air pollution episodes are normally characterised by elevated levels of more than one pollutant. This report discusses the type of air pollution episodes that occur in the United Kingdom, their likely health effects, the advice that should be given, and the actions that should be taken during these episodes.

Episodes of air pollution occurring in the United Kingdom

8.2 Episodes of air pollution fall into three general categories: a summer smog (Type 1), a vehicle smog (Type 2), and a winter smog (Type 3). Indicator pollutants are denoted for each type of episode.

8.3 The main, or indicator, pollutant associated with Type 1 episodes is ozone, with contributions from oxides of nitrogen or particles on some occasions. Ozone is formed indirectly, in the presence of sunlight, from pollutants emitted from vehicle exhausts, from industrial processes, or from evaporating solvents. Rural and urban areas may both be affected, with peak concentrations occurring in rural areas, and, because these episodes occur in the summer, they may be associated with elevated levels of aeroallergens.

8.4 Nitrogen dioxide is the main indicator of motor vehicle-associated, Type 2, episodes; levels of particles may also be increased. These episodes usually occur in urban areas and are not restricted to any one season. Because of their association with periods of calm, still weather which allow accumulation of pollutants, they tend not to occur during February and March.

8.5 Sulphur dioxide is the indicator pollutant for Type 3 winter episodes, which may also have a contribution from particles (or black smoke). These episodes are more likely to occur in areas of the United Kingdom where domestic heating adds sulphur dioxide to the pollutant mixture; motor vehicles are an important source of PM_{10} and oxides of nitrogen during these episodes. The emission patterns of the main sources restrict these episodes to certain urban locations and to the winter season, and again there is an association with stable meteorological conditions.

Biochemical and cellular effects of combinations of air pollutants

8.6 A main concern in this report has been the question of whether the biological effects of mixtures of air pollutants differ from those of the individual pollutants in isolation. The effects occurring with exposure either to a mixture or to individual components given consecutively have been considered in terms of the possibility of there being additive, synergistic or antagonistic interactions and whether any single pollutant predominates in producing effects on the respiratory tract.

8.7 Various animal experiments have investigated the effects of mixtures of actual or simulated urban pollution mixtures. It is clear that particles can induce inflammatory responses in the lung and that particles derived from diesel exhaust have a greater effect on various biological processes, including lung tumour development, than those from petrol exhausts. The most recent studies implicate the ultrafine components as being of greatest concern, in that such small particles may penetrate the respiratory epithelium and be retained in the interstitial tissue. Combined exposures to ozone and acid aerosols have demonstrated only the effects expected from ozone alone.

8.8 Exposures of animals to combinations of oxidant gases (nitrogen dioxide and ozone) have produced synergistic effects when the gases were administered concurrently at high concentrations. Sequential administration of the gases has usually resulted in additive effects. The additive or synergistic nature of the effects may be determined by the

biological endpoint being measured. Potentiation of damage (synergism) has also been seen with combinations of oxidant gases and particles, possibly due to impaired clearance of the latter. There is evidence that ozone can potentiate lung permeability effects induced by interaction between metal complexes on ultrafine particles and sulphur dioxide. The possibility of there being interactions between organic surface components of ultrafine particles and oxidising or reducing gases has received no attention.

8.9 Risk assessment of the effects of United Kingdom air pollution episodes on human health is impossible by extrapolation from the toxicological data currently available from animal experiments, which have been restricted predominantly to studies of single pollutants, often administered at high concentrations. There is a paucity of information on the toxicological effects of complex mixtures of pollutants, particularly those that relate to the three main types of pollution episode seen in the United Kingdom. The dose of pollutant required to produce biological endpoints may be different in humans and animals.

Exposure to aeroallergens

8.10 Pollen and fungal spores, or their fragments, are the main aeroallergens found in atmospheric particulate fractions between late spring and early autumn. They are responsible for hay fever and deterioration in asthma in sensitised individuals. The physiological and immunological responses to such allergens have been well studied in the laboratory. Two issues are of concern in relation to the interactions of aeroallergens with other air pollutants: the possibility that the air pollutants might exacerbate the response to allergens and the possibility that air pollutants might contribute to the development of the allergic state. This report has considered only the first of these issues.

8.11 The seasonal and geographical distribution of raised pollen and fungal spore counts means that the summer, Type 1, air pollution episode is the type most likely to occur concurrently. Chemical modification of an aeroallergen by reactive air pollutant gases could conceivably affect human response to that allergen, but there is little direct evidence that this occurs.

8.12 A limited number of studies in the laboratory in which human subjects have been exposed to relatively high concentrations of atmospheric pollutants (ozone, nitrogen dioxide, and a combination of nitrogen dioxide and sulphur dioxide) have demonstrated an enhanced reaction to inhaled aeroallergens, including some encountered indoors rather than out. This adjuvant effect has also been demonstrated in mice and humans treated with diesel exhaust-derived particles.

8.13 Epidemic outbreaks of asthma have been associated with exposure to raised levels of aeroallergens, in some cases dispersed by human activities, in others arising naturally. It is unlikely that non-biological air pollutants had an influence on the health effects occurring during these episodes.

8.14 Elevated ozone levels have been associated with increased severity of hay fever symptoms in the United Kingdom; although this does not necessarily indicate a causal relationship such a relationship is mechanistically plausible and consistent with other evidence. If individuals are very sensitive to outdoor aeroallergens it is probable that any measures that they take to reduce their inhalation exposure to these will also reduce their exposure to air pollutants.

Controlled chamber studies with combinations of air pollutants

8.15 Studies in which human subjects are exposed to controlled atmospheres of pollutant combinations in the laboratory have used either a sequential design or one in which the pollutants were administered as a mixture.

8.16 Several of the sequential studies have shown a greater response to a second pollutant following prior exposure to another pollutant rather than to clean air, although the results have been variable. When an increased response has been seen the increase has been small. This makes it difficult to determine the precise nature of the interaction, but there is no clear evidence of a synergistic interaction between any of the pollutants. An antagonistic or protective interaction was seen in a single instance, when exposure to nitric

acid or water fogs protected against the effects of ozone exposure.

8.17 In combination studies involving several pollutant gases there is no evidence that the combination produces a greater effect than would be expected from summation of the responses to individual gases. When a response has been seen the dominant effect has usually been due to ozone.

8.18 The number of studies in which subjects have been exposed to ambient polluted air in a chamber is limited. The data suggest that, in Los Angeles at least, ozone is the major contributor to a reduction in lung function caused by ambient air.

8.19 Very few studies have attempted to look at the interaction of gases with particles. Because of the diverse nature of particulate material it would be extremely difficult to do this in a systematic manner.

8.20 Interactions between air pollutants may have been underestimated in chamber studies due to the small size of many studies, limited duration of exposure and the confounding effects of prior exposure to ambient pollutants.

Effects on public health of exposures to combinations of air pollutants

8.21 The epidemiology of the health effects of mixtures of air pollutants is poorly developed. Pollutants tend to be analysed separately and some pollutants are rarely measured or are poorly characterised (especially particles). Thus, there is an incomplete picture of the pattern of exposure in reported studies of health effects. There are also problems in ascertaining the actual exposure of the population under study, and the dose received by the lung.

8.22 Even where the pattern of exposure is reasonably well described, analyses have tended to be in terms of individual pollutants rather than of mixtures; so far, little progress has been made in developing indices of mixed pollution exposure.

8.23 Since studies from the United Kingdom are still limited it has been necessary to extrapolate from studies elsewhere. Most confidence has been placed on recent studies where the emission sources and weather conditions are reasonably similar to those in the United Kingdom, *i.e.* studies from Europe in particular. If all air pollutants produced similar types of public health effects, as has been suggested for particles of differing composition, extrapolation would be possible to a greater extent. In general this is not unreasonable since the lung has a limited range of responses to particles and toxic gases; however, differences do occur, especially as regards the airway response to ozone and sulphur dioxide.

8.24 Three types of research design are available for examining short term effects but all have methodological weaknesses which must be considered when examining the evidence for a statistical association and causal relationship.

8.25 Episode studies are essentially one-event analyses of major air pollution episodes. They are subject to low statistical power, confounding (*e.g.* by temperature) and coincidental influences (*e.g.* concurrent respiratory epidemics). Nevertheless, the design of episode studies is easy to understand and their results are directly relevant to policy concerning standards and medical advice during episodes.

8.26 The evidence from episode studies that air pollution episodes in the United Kingdom may cause adverse health effects is reasonably convincing. Studies from the United Kingdom and Europe indicate that adverse health effects may occur in the winter pollution conditions which can arise in the United Kingdom. When health effects occur during such episodes, they usually involve subjects (mainly older persons) with advanced cardiorespiratory disease. There are no published studies of the effects of single summer ozone episodes in the United Kingdom, but unpublished data indicate that hospital admissions and mortality increased during the 1976 episode. While consistent with an effect of ozone, high temperatures could also have been responsible.

8.27 The results of panel studies are particularly important for determining the effects of air pollution on lung function and changes in symptoms or treatment requirements in subjects with pre-existing lung disease. The evidence suggests that all the three main types of pollution mixtures encountered in the United Kingdom are likely to be associated with small mean reductions in lung function. The evidence is probably strongest for ozone-related pollution. In healthy subjects, symptoms are unlikely and there is no clear evidence that asthmatics are especially susceptible. There is considerable variability in the response between subjects, and some subjects with a pre-existing respiratory problem might become symptomatic, or if already symptomatic, worse than previously.

8.28 Time-series studies using aggregated data, such as hospital admissions, also suggest that health effects may be associated with levels of pollution which can occur in the United Kingdom. The evidence is best for particles, which are a component of both nitrogen dioxide- and sulphur dioxide-associated winter pollution and which will also be present during still weather in summer. While there is some evidence that low levels of particles alone may have health effects, there is less certainty about the effects of nitrogen dioxide and sulphur dioxide alone and at low levels. Ozone-related pollution may also be important. There is little evidence relating to the possible interactions, if any, between the various pollutants.

8.29 Possible effects of exposure to background levels of particles or to increases in the levels of particles, as occur in the United Kingdom and which may be marked during air pollution episodes, have been considered in more detail in the report of the Department of Health's Committee on the Medical Effects of Air Pollutants (COMEAP) entitled 'Non-Biological Particles and Health', currently in press.

8.30 Taking all the evidence for acute effects together, it is concluded that episodes of air pollution which now occur in the United Kingdom from time to time (as discussed in Chapter 3), whether characterised by ozone, nitrogen dioxide, sulphur dioxide or particles, may have small acute effects on lung function in healthy subjects and may cause a worsening of cardiorespiratory disease in people with existing problems. Effects could also be occurring at levels of pollution below those experienced in air pollution episodes.

Discussion of the effects upon health of exposure to air pollution episodes in the United Kingdom

8.31 In earlier reports of the Group a number of factors likely to affect the response of individuals to air pollutants have been taken into account when attempting to predict the likely effects of exposure. They are equally valid when considering exposure to combinations of air pollutants and are summarised below:

(i) Characteristics of the exposed subject:

- age
- sex
- state of health: particularly as regards diseases such as asthma, chronic obstructive pulmonary disease and chronic cardiac failure
- individual sensitivity
- physiological state: resting or exercising, if the latter, at what level and whether breathing is predominantly nasal or oral
- history of prior exposure to pollutants: detailed information regarding the pattern of exposure and the date of the last exposure.

(ii) Characteristics of the exposure as regards various pollutants:

- concentration: steady or variable
- duration of exposure

- pattern of exposure: single or repeated episodes.

(iii) Associated characteristics of the exposure:

- ambient temperature
- humidity
- presence of other substances, *e.g.* allergens in the air.

(iv) Means of identifying or reporting effects:

- reporting of general state of health
- reporting of symptoms
- changes of lung function
- changes in use of medication
- attendance at general practitioners' surgeries or hospital accident and emergency departments
- hospital admissions
- mortality.

8.32 There are, at present, insufficient data to determine the relative importance of the factors listed in (i) to (iii) above when attempting to predict responses accurately, either in individual subjects or in particular climatic conditions.

8.33 This report has considered the health effects of pollution episodes in terms of the type of episode rather than in terms of the individual pollutants and has examined, specifically, the possibility of interactions. As indicated above (paragraphs 8.2-8.5), ambient air pollution episodes in the United Kingdom can be divided in broad terms into three main types:

- photochemical summer episodes with high levels of ozone and sometimes oxides of nitrogen and particles;
- episodes arising in the urban environment in which oxides of nitrogen derived from vehicle exhausts predominate, often associated with elevated levels of particulate matter and carbon monoxide;
- episodes occurring in a few specific localities in which sulphur dioxide is combined with particles and oxides of nitrogen.

Do short term episodes of air pollution in the United Kingdom affect the health of normal individuals?

8.34 The evidence suggests that all three main types of pollution mixtures encountered in the United Kingdom may cause small mean reductions in lung function during episodes. The evidence for this is probably strongest for ozone-related pollution. Reductions in lung function and development of symptoms during high ozone episodes are more likely to occur in those who exercise vigorously. There is no evidence that any of the three types of episode commonly seen in the United Kingdom have an acute effect on the health of people who are otherwise well.

Do short term episodes of air pollution in the United Kingdom affect the health of persons with respiratory disease?

8.35 It is likely that short term episodes of air pollution in the United Kingdom will produce adverse health effects in some persons with chronic respiratory disease. There is also evidence that some patients with asthma will find that their asthma is less well controlled. The association between elevated levels of particles and premature deaths is discussed in detail in the COMEAP report entitled 'Non-Biological Particles and Health', which is currently in press.

Are any particular groups of the population at significantly increased risk of adverse health effects?

8.36 The elderly with cardiorespiratory disease are likely to be most affected by episodes of air pollution. This was the age group which showed a significant increase in mortality and morbidity at the time of the December 1991 episode in London in which nitrogen dioxide and black smoke were increased. The increase in adverse health events is likely to have been caused by the increase in air pollution but, if so, the relative effects or interactions of black smoke and nitrogen dioxide are not clear. Evidence from the United States would fit with particles having the greater effect. If this is correct, pollution episodes in which sulphur dioxide and particles are increased would be expected to have similar effects on patients with chronic lung disease.

8.37 There is no evidence that any group other than those with lung disease are likely to be adversely affected by air pollution episodes, at pollutant levels commonly occurring in the United Kingdom, apart possibly from patients at risk from heart disease. There was a very small increase in cardiac deaths in the December 1991 pollution episode in London. The reason for this is not clear and whether it occurred in patients with pre-existing disease has not been determined.

8.38 Perhaps surprisingly, the effects of air pollution episodes on persons with asthma have proven difficult to demonstrate. This may be because asthmatic patients increase their treatment to compensate. Patients with asthma have shown an increase in hospital admissions and fall in lung function at the time of air pollution episodes in some studies but not in others. The factors which determine whether asthmatic patients are affected are uncertain though there is some evidence to suggest that those with severe asthma may be more sensitive than those with mild disease. Patients with asthma are more sensitive to sulphur dioxide than non-asthmatic subjects and patients who are particularly sensitive to sulphur dioxide would be likely to experience a temporary deterioration in their asthma during episodes when sulphur dioxide concentrations are high. There is some evidence from the United Kingdom of a small increase in hospital admissions when sulphur dioxide levels are high, although the main effect was seen in patients with other chronic respiratory diseases.

Is exposure to episodes of air pollution such as occur outdoors in the United Kingdom likely to contribute to the development of chronic disease?

8.39 Evidence relating to the long term effects of exposure to such episodes of air pollution as occur in the United Kingdom is not available. There is some evidence from other countries which suggests that long term exposure to elevated concentrations of pollutants may increase the risk of death from chronic cardiopulmonary disease. The extent to which this relates to average exposure or to exposure to multiple episodes of high concentrations is uncertain as the two are likely to be correlated. In a report by COMEAP entitled 'Asthma and Outdoor Air Pollution' the weight of evidence suggested that air pollution did not contribute to the initiation of asthma.

8.40 Much of the recent work on the chronic effects of pollutants on public health has been carried out in the USA and specifically relates to long-term exposure to particulate material. The health effects of particles have been reviewed by COMEAP; their report, entitled 'Non-Biological Particles and Health' is currently in press.

Giving advice on air pollution episodes

8.41 The Advisory Group recommends that information on air quality should be available to the general public, as should information on the possible health consequences of air pollution episodes. The remit of MAAPE has been to consider the effect of episodes of air pollution and the advice that should be given to the general public and to vulnerable groups when such episodes occur. Before proceeding to consider the nature of the advice that might be given during episodes of air pollution, the Group has considered how such episodes may best be described.

Description of air pollution episodes

8.42 The Advisory Group discussed the possibility of using a single index value as a descriptor of an episode. The conclusions in this report are largely based on epidemiological data in which the outcome has been related to a single indicator pollutant rather than an index value summating the different pollutants which could have contributed to the effect. Evidence from analysis of chamber and epidemiological studies suggests that the effects of air pollutants on human health are likely to be additive and that synergistic effects are unlikely. Although index values are in use in some countries,

members felt that these were cumbersome and were not convinced that they would be any better than using the indicator pollutant to describe the types of air pollution episode that may occur in the United Kingdom.

8.43 The system currently in use by the Department of the Environment involves the description of *air quality* in terms of the concentrations of individual pollutants, *e.g.* ozone, sulphur dioxide and nitrogen dioxide, by means of a series of descriptors: **"Very Good"**, **"Good"**, **"Poor"** or **"Very Poor"**. Earlier reports of the group have recommended that the description of *air pollution* as **"Low"**, **"Moderate"**, **"High"**, or **"Very High"** would be very much more appropriate to the provision of advice. The Advisory Group reiterates this view, but, to avoid confusion, discussion of a means of defining episodes will be couched in terms of the current, **"Very Good"** to **"Very Poor"**, descriptor series.

8.44 Identification of an air pollution episode may be done for two reasons: firstly, as a prediction or forecast that one will occur in the near future and, secondly, as information that one is occurring or has occurred. Predicting an episode is important if it allows individuals to alter their usual behaviour patterns either to avoid increased exposure or to reduce their contribution to pollution sources. Since the minimum period over which a person can easily modify their behaviour pattern is probably one day the Group considered that air pollution episodes should be forecast or recorded in terms of 'episode-days'.

8.45 Various types of episode are described in Chapter 3 and the Group addressed the question of what information should be provided in any forecast or record of an episode. It was agreed that the following points should be included to allow an individual to make an informed decision about their actions during an air pollution episode:

- *Type of episode*, using the descriptors "Summer smog", "Vehicle smog" or "Winter smog";
- *Indicator pollutant*, ozone, nitrogen dioxide or sulphur dioxide respectively;
- *Other pollutants* associated with the episode, *e.g.* particles (PM_{10});
- *Geographical location, e.g.* local, city-wide or regional;
- *Severity of the episode*, this descriptor is discussed below (see paragraphs 8.49-8.51) and
- *Duration*, in terms of episode-days.

8.46 A hypothetical example of the type of forecast which is desirable is provided below:

- An episode of summer smog is expected across much of southern England during the coming two to three days. Levels of pollutants, especially ozone, may be raised, most markedly in the afternoon and early evening. Air quality is expected to enter the **"Poor"** band.

8.47 The prediction or recording of an episode at a particular location requires that there be an ambient concentration of the indicator pollutant which is expected to be, or has been, exceeded. The Group agreed that the transition points between the **"Good"** and **"Poor"** bands of the Department of the Environment air quality banding system should be used to define an episode. These transition points (hourly average concentrations) for ozone, nitrogen dioxide and sulphur dioxide are currently 90, 100 and 125 ppb (180, 188, and 357 $\mu g/m^3$) respectively.

8.48 For ozone, the transition point corresponds to the European Community Directive level at which public information should be provided. The value for sulphur dioxide is similar to the current World Health Organization (WHO) 1-hour health guideline. The nitrogen dioxide value is lower than the current WHO 1-hour health guideline of 210 ppb

(395 µg/m^3), and is also lower than the value of 300 ppb (564 µg/m^3) at which this Group recommended, in its report on Oxides of Nitrogen, that public health advice should be provided. However, a recent meeting of experts involved in updating the WHO Air Quality Guidelines recommended that the 1-hour guideline for nitrogen dioxide should be lowered from 210 ppb to 100 ppb (395 to 188 µg/m^3).

8.49 The Group considered what characteristics of an episode might lead to it being described as "Severe". Possible factors might be that:

- The concentration of a pollutant had entered, or was expected to enter, the **"Very Poor"** band;
- Two or more pollutants had reached, or were expected to reach, the **"Poor"** band;
- The episode had persisted, or was expected to persist, over a period of more than one day.

8.50 It was recognised that occasions when two pollutants would both reach the **"Poor"** band are likely to be infrequent and that the evidence for synergistic, or even additive, action of air pollutants is relatively weak; the second option was therefore discarded. Although some episodes can persist or re-occur on consecutive days it was felt that the most important determinant of severity was likely to be the observation or prediction of an increase of a pollutant level such that it would reach the **"Very Poor"** band. This criterion is therefore recommended, though it is accepted that there is a lack of data on the relative importance of the duration of episodes as compared with the peak concentrations reached.

8.51 It is accepted that categorising episodes in which a number of air pollutants may be at elevated concentrations for varying periods is difficult and that no descriptor is likely to be entirely satisfactory. However, the use of the term "Severe" allows those predicting the episode some latitude or use of judgement in making their forecast of the episode.

The provision of health advice

8.52 In deciding on the nature of the advice that should be available account was taken of several factors, including the level of uncertainty in current knowledge of the health effects of high pollution episodes seen nowadays in the United Kingdom. The Group also recognised the fact that, for the great majority of people, the observed effects have been minimal at the concentrations of pollutants seen currently.

8.53 Some groups, such as those with asthma and other chronic diseases, are in general more likely to be susceptible to adverse effects from high pollution episodes, although it is still difficult to predict within such populations which individuals are likely to be affected by an air pollution episode.

8.54 If advice is to be beneficial for the general public or for particular groups then, ideally, the following criteria should be met:

- That acute episodes of air pollution can be predicted ahead of time so that the people at risk are able to take appropriate action;
- That advice can be targeted at the groups at risk;
- That there are interventions that are known to work in those at risk;
- That giving warnings and advice does not induce anxiety or counter-measures that diminish or negate the beneficial effects achieved by appropriate interventions in the groups at risk.

8.55 The Group considered each of these in relation to current knowledge of air pollution episodes.

Ability to predict an acute episode of high pollution

8.56 The larger recent air pollution episodes in the UK have lasted for a few days so that it is possible to alert the population at the beginning of an episode if not before it.

Identifying vulnerable groups

8.57 Certain groups have been identified as being at increased risk from episodes of air pollution, either because they are more sensitive to the pollutant (asthmatic patients, for example, are more responsive to sulphur dioxide) or because they have worse lung function to start with, so that the effect of any further deterioration is greater. Additionally patients with advanced cardiovascular disease may be at increased risk. The increased mortality seen in some episodes of high ambient pollution appears to have mainly affected patients with severe lung disease; to some extent, an imminent death being brought forward by the episode of air pollution. Although admissions for asthma and attacks of asthma have increased during some air pollution episodes, in others this has not occurred. The Group recognised that the majority of patients with chest disease, including those with asthma, show only a small deterioration in lung function, if any, during air pollution episodes.

8.58 The Advisory Group recognised that patients with cardiac problems may be affected during air pollution episodes. However, so little is known about which patients are at risk, the mechanisms of effect or whether any intervention would be beneficial that the Group does not recommend specific advice with respect to cardiac problems during air pollution episodes.

Are there known interventions that will prevent the adverse effects of air pollution episodes?

8.59 Because it is not possible at present to identify those patients with asthma or chronic lung or cardiovascular diseases who are at particular risk during an acute pollution episode, advice has to be provided to all patients with asthma and chronic cardiorespiratory problems. The main interventions available during an air pollution episode are to advise patients to spend less time exercising out of doors or to modify their treatment.

Reducing exercise and spending less time out of doors

8.60 Levels of ozone and sulphur dioxide are higher out of doors and the effects of inhaling ozone and sulphur dioxide on lung function are greater when subjects exercise, as more pollutant is then inhaled. Whether restricting the activity of children or adults during an episode of air pollution is feasible or beneficial in practice has not been studied. Patients with more severe lung disease are less able to exercise and are likely to spend more time indoors.

8.61 Nitrogen dioxide differs from other pollutants in that concentrations may be higher indoors than outdoors depending on the type of heating and cooking appliances in the home and whether tobacco is smoked. There is no evidence that the effects of nitrogen dioxide are increased by exercise (and some evidence suggests that the reverse may be true).

Modifying drug treatment

8.62 For patients with asthma it is likely that an increase in the dose from their preventative inhaler would counteract the adverse effects seen during an air pollution episode, although this has not been studied. Using a ß-agonist "reliever" inhaler would be likely to reverse some of the effects of pollution. It has been suggested by others that all patients on medication for asthma or chronic obstructive lung disease should increase their preventative medication during an air pollution episode, but, since only a small proportion of asthmatic patients are likely to be adversely affected during an episode, many patients would increase their medication unnecessarily. Episodes of pollution are only one of many factors that trigger asthma attacks and probably occur less frequently than other factors including raised levels of allergen, viral infections and, possibly, thunderstorms. Because there are many triggers and asthma exacerbations are unpredictable, patients are encouraged to adjust their inhaled medication according to their symptoms and peak expiratory flow. Continuing this approach during an air pollution episode would mean that only patients affected by the air pollution would increase their treatment. This approach is recommended.

That the advice and/or interventions do not increase anxiety inappropriately or cause adverse effects in some subjects

8.63 There is evidence that asthmatic children are generally less fit than they might be and, for both physical and psychological reasons, asthmatic children are strongly encouraged to participate in sport and normal activities as much as possible. Suggesting that asthmatic children should restrict their activities on high pollution days could undermine this message and emphasise their difference from other children. Because of its unpredictable nature, asthma inevitably causes some anxiety amongst patients and parents of children with asthma; any advice must provide a fair and realistic assessment of any increased risk (or lack of it) during an air pollution episode. Many children who often get asthma on exercise take preventative medication beforehand. Therefore, no additional measures, other than those of paragraph 8.62, are recommended for them.

8.64 The Advisory Group has taken many factors into account when considering what advice should be given to the public and to vulnerable groups during an episode of air pollution. There is no information on the effect of curtailing exercise or modifying treatment for vulnerable groups during an air pollution episode. Giving such advice could be counterproductive and it therefore needs to be assessed before being recommended widely. As more information becomes available the advice given to vulnerable groups may need to be modified. It is recommended that the Department of Health's Committee on the Medical Effects of Air Pollutants keep this under review.

Should the public be recommended to use smog masks during an air pollution episode?

8.65 The Terms of Reference of the Advisory Group specify that it should consider whether advice on personal protective measures should be given by Central Government during episodes of air pollution. One point of relevance is whether the population at risk should be advised to use smog masks. In previous reports this has not been advised. There is evidence that some smog masks, when used appropriately, can reduce exposure to certain pollutants, although, in practice, not enough is known as to how well they work. Their efficiency has improved but, because they may hinder the breathing of persons whose lung function is already impaired, the Group does not specifically recommend their use.

Terms of public health advice during air pollution episodes

8.66 The current advice on health given on the FREEPHONE Air Quality Helpline is:

'The following advice on health applies on days when air quality is **"Poor"** or **"Very Poor"**. If you have a breathing problem, such as asthma or bronchitis, you may feel a little uncomfortable on these days. You might cough and feel some pain when breathing deeply. It might help to increase your treatment temporarily — you should talk to your doctor about the options.'

8.67 It is recommended that this advice be modified as follows:

'The following advice on health applies only on days when air quality is **"Poor"** or **"Very Poor"**. If you have a chest problem, such as asthma or bronchitis, you may experience a worsening of your symptoms on these days. If this is the case it might help to increase your treatment temporarily – you should talk to your doctor about the options.'

8.68 It is recommended that the findings of this report be drawn to the attention of doctors.

8.69 The Advisory Group has considered which research objectives, in the United Kingdom, might lead to a better understanding of the health effects of population exposure to episodes of air pollution: those identified are listed as a series of recommendations for research in Appendix 1.

Appendix 1

Recommendations for Further Research

A1.1 All the data used in the analysis of air pollution episodes in this report were obtained from ambient fixed point monitoring stations. As a result, their relevance to the exposure of individuals in the population and the resulting health impacts is indirect. Additional work is needed on:

- Personal exposure to pollutant mixtures during episodes, assessed directly using personal monitors;
- Establishing personal exposure during episodes from statistical modelling of ambient and indoor measurements;
- Measuring the ratios of indoor to outdoor concentrations of pollutants during episodes;
- Assessing the spatial variability of pollutant concentrations in urban areas during episodes;
- Detecting micro-environment 'hot-spots' in urban areas, *e.g.* at kerbsides, within cars, at petrol filling stations *etc.*;
- Establishing the relationship between exposure assessed on the basis of fixed point measurements and actual personal exposure.

A1.2 In addition, there is a need for further characterisation of the minor components of the pollutant mixture that occurs in busy streets, notably during periods in which there are raised concentrations of the 'classic' pollutants.

A1.3 In order to understand the mechanisms by which complex toxic mixtures interact with the respiratory tract there is a need for basic research on the normal functions of, and protective mechanisms operating in, respiratory tract tissues.

A1.4 Much of the data used in assessing the risks in humans of exposure to air pollutants is obtained from experiments with laboratory rodents. Consequently, there is a need for more information on interspecies variation in order to define which animal species will prove the best surrogate for studies of complex pollutant mixtures relevant to human exposure.

A1.5 In studies which address the endpoints of damage by air pollutants there is a need to determine whether these endpoints are transient or persistent, and whether there is any temporary or permanent impairment of health.

A1.6 Studies in animals or cellular systems should utilise a protocol which is relevant to human exposure. This would require variation in the concentrations and mixtures of pollutants and should also reflect the variations (of age, gender, or state of health) that exist in human populations.

A1.7 There is a paucity of information on the mechanisms of toxic action of the ultrafine components of suspended particulate matter. The dependence of toxicity on the physical and chemical properties of this material is a topic which could be best addressed by studies using rodent or human cell cultures.

A1.8 In order to clarify the rôle of air pollutants in the expression of the human response

to aeroallergens there is a need for further research in various areas:

- the patterns of co-occurrence of air pollutants and aeroallergens (the latter to include the important allergenic micronic or submicronic fragments of pollen);

- controlled human studies of the interactions between allergen challenge and exposure to pollutant concentrations typical of United Kingdom episodes;

- epidemiological studies specifically designed to investigate the interactive effects of air pollutants and aeroallergens on populations in the United Kingdom;

- further studies to elucidate the mechanisms which underly these interactions. These studies should encompass not only the immunological responses of human subjects, but also the chemical and physical interactions between allergens and pollutants in the atmosphere.

A1.9 In chamber studies designed to detect additive, synergistic, or antagonistic interactions of air pollutants there is a need for studies in which larger number of subjects are included, particularly in cases where it appears that there is considerable variation in response.

A1.10 There should be a greater emphasis on the determination of dose-response curves. Although this would increase the complexity of the study, there would be a better chance of detecting an interaction.

A1.11 Chamber studies should be of longer duration in order to minimise the effects of prior exposure to ambient pollutants.

A1.12 There is a need for additional studies investigating the possible interactions of pollutant gases with particles. The technical difficulties in carrying out such investigations have limited the number which have been done.

A1.13 This report has identified some deficiencies of previous epidemiological studies in the United Kingdom; a particular problem has been the limited numbers of studies which have investigated the health effects of the current forms of air pollution. There is a need for studies of Type 1, ozone, episodes in the summer months, providing that there is adequate allowance for the health effects of high temperatures.

A1.14 In addition, the epidemiology of the health effects of mixtures of air pollutants is poorly developed and a more complete picture of the pattern of exposure to all pollutants, gases and particles, is required. Specifically, there could be studies of groups of individuals, identified as being liable to be exposed to traffic-related pollutants, with a view to studying variations of symptoms or lung function on a daily basis during periods when there was a probability of Type 2, motor vehicle-related, episodes occurring.

Appendix 2

Glossary of Terms and Abbreviations

A&E	Accident and Emergency
Aeroallergen	Airborne antigen that causes allergy in a sensitive individual, *e.g.* pollen, house dust mite
Anthesis	Time of opening of the flower
Autacoids	Locally active hormones
BAL	Bronchoalveolar lavage
Black smoke	A method of measuring fine particles in which the concentration is estimated by quantitating the blackness of the stain produced on a filter paper through which air has been drawn
CAMs	Cell adhesion molecules
CD4⁺	Cell surface protein on T-lymphocytes which acts as a specific receptor (CD: cluster differentiation)
CMO	Chief Medical Officer
CO	Carbon monoxide
COMEAP	The Department of Health's Committee on the Medical Effects of Air Pollutants
COPD	Chronic obstructive pulmonary disease
Cytokines	Proteins which stimulate or inhibit the differentiation, proliferation or function of immune cells and other cells. Have autocrine/paracrine activity
Dendritic cell	Antigen-presenting cell, related to macrophages. Depending on site may be identified as an M-cell, veil cell, or Langerhans cell
DEP	Diesel exhaust particles
DH	Department of Health
DoE	Department of the Environment
E-Selectin	A molecule involved in the initiation of adhesion of leucocytes to endothelial cells
EC	European Community
Endothelin-1	One of a class of factors released which play a rôle in controlling vascular smooth muscle. First demonstrated in endothelial cells
EPAQS	Expert Panel on Air Quality Standards
FcεRI	Receptor for IgE (*qv*) found on mast cells and basophils

FcεRII	Receptor for IgE (*qv*) found on eosinophils, monocytes/ macrophages and platelets
FEV_1	Volume of air expired during the first second of a maximal or "forced" expiration
FVC	Forced vital capacity
GM-CSF	Granulocyte-macrophage-colony-stimulating factor: a cytokine
GP	General practitioner
HLA	Human leucocyte antigen
ICAM-1	Intercellular adhesion molecule 1
IFN-γ	Interferon-gamma, an interferon involved in the regulation of the immune response, a cytokine
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-3	Interleukin-3
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-6	Interferon-ß2 (formerly Interleukin-6)
IL-8	Interleukin-8
IL-9	Interleukin-9
IL-13	Interleukin-13
Indicator pollutant	The air pollutant which, in this document, is used to define the generic type of an air pollution episode
INF	Interferon
IR	Infrared
LTC_4, LTD_4	Leukotriene C_4 and D_4, substances that cause contraction of some types of smooth muscle, especially bronchial muscle, and increase vascular permeability
Mast cells	Cells which, when cross-linked by antigen to IgE, mediate an immune response. These cells produce histamine and cytokines (*qv*)

MHC	Major histocompatibility complex. A genetic region encoding molecules involved in antigen presentation to T-lymphocytes
MMD	Mass median diameter
MMEF	Maximum mid-expiratory flow
NO	Nitric oxide, properly called nitrogen monoxide
NO_2	Nitrogen dioxide
NO_X	Total oxides of nitrogen. Conventionally the mixture of NO and NO_2 in the atmosphere
O_3	Ozone
P-Selectin	A molecule involved in the initiation of adhesion of leucocytes to endothelial cells
PAF	Platelet activating factor
PAN	Peroxyacetyl nitrate
PaO_2	Arterial oxygen tension
$PC_{20}FEV_1$	Provocation concentration 20: the concentration of a test agent which produces a 20% fall in FEV_1 (*qv*)
PC_{100} sRaw	Provocation concentration causing a 100% increase in specific airway resistance
$PD_{20}FEV_1$	Provocation dose 20: the dose of a test agent which produces a 20% fall in FEV_1 (*qv*)
PD_{35} sGaw	Provocation dose causing a 35% fall in specific airway conductance
PGD_2	Prostaglandin D_2
PM_{10}	Particulate Matter (10 μm): term applied to suspended particulate matter with an aerodynamic diameter of less than 10 μm
ppb	Parts per billion, 1 part by volume in 10^9
ppm	Parts per million, 1 part by volume in 10^6
PV_{100} sRaw	Provocative ventilation causing a 100% increase in specific airway resistance
RANTES	Regulated upon Activation, Normal T-cell Expressed and Secreted: a cytokine
Raw	Airway resistance
Rhinorrhoea	Discharge of mucus from the nose
RSP	Respirable suspended particulates

sGaw	Specific airway conductance
SO_2	Sulphur dioxide
SO_X	Oxides of sulphur
SP	Suspended particles
SPM	Suspended Particulate Matter
sRaw	Specific airway resistance
Stem cell factor	Factor capable of stimulating the differentiation and proliferation of stem cells
TEOM	Tapered Element Oscillating Microbalance, an instrument for the continuous measurement of suspended particulate matter, typically PM_{10}, in ambient air
T Helper cells	Subpopulation of lymphocytes originating in the thymus (hence T-lymphocytes) which recognise and bind to antigen plus MHC (*qv*) molecules and produce cytokines (*qv*) which switch on the immune response
Th1, Th2	Two subpopulations of T helper cells (*qv*)
TLC	Total lung capacity
TNF-α	Tumour necrosis factor-alpha
TNF-β	Tumour necrosis factor-beta
TSP	Total suspended particles
UV	Ultraviolet
VCAM-1	Vascular cell adhesion molecule 1
WHO	World Health Organization
95% CL	95% Confidence limits; the range of values within which there is a 95% chance of the true result falling
98th Percentile	The point on a frequency distribution below which 98% of observations lie

Conversion Factors

NO	1 ppb = 1.25 $\mu g/m^3$	1 $\mu g/m^3$ = 0.800 ppb
NO_2	1 ppb = 1.88 $\mu g/m^3$	1 $\mu g/m^3$ = 0.532 ppb
O_3	1 ppb = 2.00 $\mu g/m^3$	1 $\mu g/m^3$ = 0.500 ppb
SO_2	1 ppb = 2.86 $\mu g/m^3$	1 $\mu g/m^3$ = 0.350 ppb

Appendix 3

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