Medical Research Council

Institute for Environment and Health

IEH report on

'AIR POLLUTION AND RESPIRATORY DISEASE: UK RESEARCH PRIORITIES'

THIS PUBLICATION IS BASED ON A WORKSHOP HELD IN LEICESTER
28 FEBRUARY 1994

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The Institute for Environment and Health, was established by the Medical Research Council adjacent to the Interdisciplinary Research Centre on Mechanisms of Human Toxicity at the University of Leicester in 1993. The Institute is partly funded by the Department of the Environment and the Department of Health by way of specific research and consultancy contracts.

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The Workshop was chaired by Professor Anthony Newman Taylor, who is Chairman of the Medical Research Council Committee on Toxic Hazards in the Environment and Workplace Aetiology of Asthma Working Group.

The views expressed in the Workshop report are those of the Workshop participants, and do not necessarily represent those of any Government Department or Agency.

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Foreword

The origins of the Institute for Environment and Health (IEH) can be traced to the Department of the Environment and the Department of Health, who wished to see the establishment of an institute which could act as a focus for the diverse range of resources addressing issues concerned with environment and health. In determining environmental quality standards and identifying knowledge gaps which frustrate a proper analysis of environmental health problems there was a specific need to strengthen understanding of the health effects of pollution.

Towards the end of 1993 the Medical Research Council (MRC) confirmed its support for a new Institute for Environment and Health which would have as its mission the promotion of a healthier environment by facilitating information exchange, identifying and evaluating environmental health issues and managing research programmes on the adverse effects of chemicals. In doing so it was hoped that this would lead to a better understanding of the risk to human health and the environment resulting from exposure to hazardous substances in air, water and soil.

Clearly the range of problems and issues associated with environment and health meant that the IEH would have to establish priorities for its strategic objectives. These included acting as a co-ordination centre on chemicals in the environment and focusing on associations between environmental pollution and risks to human health. Also, the IEH will act as a primary contact point for international initiatives in the field of environment and health and will be instrumental in the identification of disease conditions which may be caused by, or influenced by, exposure to environmental chemicals. The IEH will publish authoritative scientific assessments and reports on subjects of major topical interest and significance.

The siting of the IEH in Leicester immediately adjacent to the Interdisciplinary Research Centre for Mechanisms of Human Toxicity has given the Institute access to approximately 200 scientists and support staff working on toxicology research problems. The MRC has relocated its Toxicology Unit from Carshalton to the Centre. There is opportunity for the Toxicology Unit to act, at least in part, as a technical resource for the IEH as well as providing a valuable source of toxicological expertise, thus strongly complementing the work of the Institute. Furthermore, the location of the IEH within the University of Leicester campus

provides access to medical scientists and basic scientists involved in problems which are allied to or relevant to human health issues of concern to the Institute.

As the first director of the IEH, I am confident that this initiative taken by the MRC in conjunction with the Department of the Environment and the Department of Health offers an exciting and challenging future for all those involved. More importantly, we have the opportunity to establish an institute that can use the most appropriate intellectual and technical skills to evaluate, in an objective and rational manner, important problems concerning the environment and health. In so doing, the IEH will inform and influence those bodies charged with delivering policies which can protect and improve the environment in which we live.

The publication of this report marks an important development in collaboration between the Departments of Environment and Health and the MRC since it defines a comprehensive research programme on air pollution and respiratory disease for the UK covering the interests and needs of all three groups.

Professor Lewis Smith
Director
Institute for Environment and Health August 1994

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Report summary

This report, which was prepared at the request of the Department of the Environment and in collaboration with the Department of Health, presents a review of research priorities for the UK, on air pollution and respiratory disease, and a recommended programme of research in the field.

A report is included of a workshop which was convened to provide advice, in the light of previous recommendations by Government department and Medical Research Council expert groups, on what research should be undertaken to investigate the relationship between air pollution and respiratory disease in the UK.

The research priorities identified during the workshop are presented in the form of ten key issues. Together these form a proposed comprehensive research programme into the relationship between air pollution and respiratory disease, which has been developed by the Institute for Environment and Health in collaboration with the workshop participants. The report also includes within the context of the proposed research programme an analysis of recommendations for research previously identified by various UK expert groups.

The workshop identified a number of issues of concern, which can be divided into three principal groups: two aetiological and one methodological. These are: (a) acute or proximate affects of exposure to air pollutants; (b) long-term consequences of exposures to indoor or outdoor air pollutants; and (c) monitoring, and characterisation of pollutants, exposures, and measures of adverse health effects.

Concerning the acute effects of exposure to air pollutants, the programme envisages that epidemiological studies would help in the assessment of the relationship between background levels of pollution, short-term changes in patterns of pollution, and acute respiratory disease. Other studies should include assessments of the effects of mixtures, and investigations of the mechanisms involved in the toxicology of the acute effects.

The longer-term consequences of exposure to air pollutants may also require some epidemiological studies, which might be cross-sectional or cohort. The possible effects of both long-term exposures and single or multiple short-term exposures, for example at vulnerable periods such as in childhood, should be considered. Investigations of the mechanisms involved in the development of chronic health effects are also recommended.

The methodological issues recommended are the development of personal sampling methods, further characterisation of particulate air pollution occurring in the UK, and characterisation of exposure-response relationships and of measures of the physiological and pathological responses to airborne pollutants.

Introduction

This is the second in a series of reports to be published by the MRC Institute for Environment and Health (IEH). One of the issues being addressed by the IEH is the link between air pollution and ill-health; the first '*IEH Report*' considered some of the uncertainties involved in evaluating the effects of air pollution on health (IEH, 1994).

This report was prepared at the request of the Department of the Environment and in collaboration with the Department of Health to:

- consider all existing recommendations and proposals for research on links between air pollution and health, excluding cancer, made by expert advisory groups in the field
- identify gaps in current knowledge about the links between exposure to environmental chemicals and respiratory ill-health and make additional proposals for research to fill these gaps
- reach scientific consensus on the research proposals, set research priorities and develop them into a definitive and workable programme.

As part of the project, experts in the field were invited to a 'Workshop on air pollution and respiratory disease: UK research priorities', which was held in Leicester on 28 February 1994.

The characteristics of air pollution episodes have changed following the introduction of smokeless fuel for domestic heating and the increase in traffic. The large number of acute cardiorespiratory deaths seen during short-term pollution episodes in the 1950's in the UK no longer occurs. However, recent international data suggest that episodes of air pollution and lesser short-term fluctuations in pollutant levels may give rise to increased cardiorespiratory mortality, respiratory morbidity and temporary reductions in lung function. Furthermore, epidemiological studies from outside the UK suggest an appreciable shortening of life from cardiorespiratory disease with increasing levels of air pollutants. The chronic health effects that have been implicated include accelerated decline in lung function and an increase in 'all cause' mortality, particularly that resulting from respiratory and cardiovascular disease. The nature of both indoor and outdoor pollution and differences in climatic conditions in the UK are such that

it is unclear to what extent data are currently applicable to this country.

There are seven advisory groups that address the issues of air pollution and adverse health effects: the Advisory Group on the Medical Aspects of Air Pollution Episodes (MAAPE), the Committee on the Medical Effects of Air Pollutants (COMEAP), the Expert Panel on Air Quality Standards (EPAQS), the COMEAP subgroup on asthma and air pollution, COMEAP subgroup on particulates, the Quality of Urban Air Review Group (QUARG) and the MRC Committee on Toxic Hazards in the Environment and Workplace (CTHEW) Aetiology of Asthma Working Group. Recommendations for research made previously by these groups are listed in Appendix 1. The workshop to review research priorities was chaired by Professor Anthony Newman Taylor, chairman of the CTHEW Working Group, and the chairmen of the other six groups were invited to provide a personal view of the knowledge gaps and research priorities in the field covered by their respective committees.

WORKSHOP DISCUSSIONS

The detailed discussions of the Workshop are set out in the Workshop Report (pp 7-27) which does not constitute a verbatim report of each of the six presentations or of the ensuing discussions. Instead, all the pertinent discussions have been summarised under a series of subject headings.

In the course of their deliberations the participants discussed whether acute or chronic effects cause more concern and whether the adverse effects of air pollution are likely to be serious in the general population or only in sensitive subgroups. There was also discussion about causes and confounders of observed health effects relationships with reference to both individual pollutants and mixtures. The participants also sought to clarify the gaps in existing knowledge and discussed some of the major barriers to successful studies. Some consideration was given as to how research findings might be applied practically and how the effectiveness of both changes in air pollution patterns and interventions might be evaluated.

The Workshop participants recognised the need for both exposure assessment and measurement of health effects in order to properly investigate the association between air pollution and respiratory disease. Although the following report concentrates on the investigation of adverse health effects, the need for appropriate air pollution monitoring is also emphasised.

RESEARCH PRIORITIES

The Workshop members evaluated the relevant issues and identified a number of areas in need of further research in the UK. These are highlighted in italics, in the Workshop Report. The priorities identified by the Workshop members were used to draw up ten areas in need of further research which comprise a comprehensive research programme. In drawing up the research programme the need to take account of both short-term and long-term exposures and the possible influence of each of these on both acute and chronic health outcomes was recognised. The research programme has been developed to advise and guide Government Departments and could be used as a basis for a research tendering exercise. It will of course be for the funding bodies to decide on what work they will commission.

Recommendations made by the committees and working groups that have previously addressed the issues of research needs in the area of air pollution and health in the UK are listed in Appendix 1. The IEH Secretariat has made an analysis of how the health-related questions from these somewhat more specific recommendations are related to the research programme outlined in the present report. The analysis of previously published recommendations for research in the UK is presented at the end of this report.

REFERENCES

IEH (1994) *IEH Report on Air pollution and health: Understanding the uncertainties*, (*Report R1*), Leicester, Institute for Environment and Health

Workshop report

PRESENTATIONS TO THE WORKSHOP

In order to be able to take into account existing recommendations and proposals made by expert advisory groups in the field, the chairmen of the UK committees and working groups that address the issues of air pollution and adverse health effects were invited to make presentations to the Workshop describing their view of where the research priorities should lie.

Professor Tattersfield (MAAPE) concentrated on the effects of short-term episodes of air pollution. MAAPE has considered the health effects of episodes of elevated concentrations of ozone (O_3), sulphur dioxide (SO_2), acid aerosols and particulates, and oxides of nitrogen (NO_x); these have been published as three separate reports with research recommendations (Advisory Group on the Medical Aspects of Air Pollution Episodes, 1991, 1992, 1993). Professor Tattersfield called for better monitoring and better data collection during episodes of high pollution. She also identified a need for improved risk assessment and more information on groups that are at risk.

Professor Holgate (COMEAP) started his presentation by commenting that not only traffic-related pollution but also, in certain local communities, industrial pollution is of concern. He called for an improvement in monitoring related to the measurement of health indices and considered that concerns about both the primary development of asthma and the increase in the number of asthma attacks should be more carefully addressed. He stressed that it is important not to neglect the effects of indoor air pollution. Professor Holgate called for better characterisation of particulates and for studies on the toxicology of PM_{10}*, and for epidemiological studies to be carried out in the UK to investigate links between outdoor air pollution and human disease morbidity. He stressed that chamber studies should be used, particularly for the development of surrogate

*PM_{10}: inhalable particles with an aerodynamic diameter of less than 10 µm

markers of airway inflammation, and called for more studies on the mechanisms whereby air pollutants might cause lung injury.

Professor Seaton (EPAQS) explained that it is the responsibility of EPAQS to recommend health-based environmental air quality standards. It has so far discussed the pollutants benzene, 1,3-butadiene, O_3, carbon monoxide, and SO_2, and its reports, on benzene and O_3 were published recently (Expert Panel on Air Quality Standards, 1994a,b). In his presentation Professor Seaton addressed the question 'Do small particles kill people?', and presented a hypothesis whereby clotting factors, which are subject to seasonal variations, might interact with the effects of ultrafine particulates to give an increased likelihood of cardiovascular death.

Professor Anderson (COMEAP subgroup on asthma and air pollution) concentrated largely on asthma. He stressed that there is a real need for epidemiological evidence on the possible link between air pollution and asthma in the UK since the mixture of air pollutants and other causal factors for asthma may well be different in the UK than elsewhere.

Mr Waller (COMEAP subgroup on particulates) noted that, in view of the reduction in ambient air pollutant levels over the past 30–40 years, it is surprising that there are still apparent adverse effects of air pollution on health. Mr Waller identified the following research priorities for particulates: better physical and chemical characterisation, an examination of the relationship between monitoring and exposure, the establishment of inhalation chambers in the UK for experimental studies, a further interpretation of recent epidemiological studies such as the US Six Cities study (Dockery *et al.*, 1993), the maintenance and exploitation of existing time-series data and the establishment of new panel studies to investigate acute effects and of cohorts to study chronic effects.

Professor Harrison (QUARG) emphasised five key issues that need to be addressed, namely (i) the possibility that air pollution might cause respiratory disease and asthma or other adverse effects on respiratory function, (ii) the possibility that air pollution might cause significant acute health effects in normal individuals and/or in those with respiratory disease and (iii) the possibility that interactions between different pollutants and other environmental factors might produce short- or long-term health effects, (iv) the ways in which people might be protected against the effects of air pollution on their health, and (v) the identification of groups who are particularly susceptible to air pollution and who are adversely affected by lower doses than 'normal' individuals.

HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS

THE HEALTH EFFECTS

AIR POLLUTION EPISODES

Short-term episodes of air pollution in which concentrations of certain air pollutants have reached notably elevated levels have been recognised in the past in the UK; a recent example is that which occurred in December 1991 in London (Advisory Group on the Medical Aspects of Air Pollution Episodes, 1993; Quality of Urban Air Review Group, 1993).

It is necessary to know both the immediate and the long-term health effects of short-term pollution episodes that have occurred in recent years in the UK. It is recognised that long-term or chronic consequences might arise from short-term exposures. For example, babies may be a particularly sensitive group and exposures occurring early in life may have long-term consequences. It is necessary to understand which pollutants are responsible for any immediate and late adverse health effects, who is at risk, the pathological mechanisms responsible for the effects and what can be done to reduce the risk.

Immediate effects can be studied by looking at either single very high pollution episodes or repeated moderately high pollution episodes. Requirements for these kinds of study include monitoring stations at relevant sites, the ability to integrate data on pollutants, climate, allergens and other confounding factors, and

good indices of outcome. It is currently possible to predict episodes of air pollution a few days in advance and this may be helpful in some investigations.

Among the important research issues are what happens in particularly high pollution episodes such as occurred in December 1991 and what are the health consequences of these episodes. *Routine data collection systems and established panels of volunteers (normal people and/or patients) should be able to provide useful data during air pollution episodes. Where possible, during such episodes, measurements of differences in FEV_1 or PEF* between groups would be helpful.*

It should be possible to establish dose-response relationships for acute effects following pollution episodes of short duration. *There should be a systematic approach to investigating all air pollution episodes; this should include a standardised protocol for describing levels of pollution and meteorological variables during the episode. There is a need for prospective studies of 'at risk' groups during pollution episodes;* these could be carried out using pre-established panels, although it was recognised that the siting of effective studies might be dictated by the location of monitoring sites.

FURTHER EPIDEMIOLOGICAL STUDIES

The lack of recent epidemiological studies on air pollution and health in the UK was noted with some concern. The first priority is to know whether or not there are acute health effects associated with current levels of air pollution in the UK. Apart from a few recent studies (e.g. Walters *et al*., 1994), the latest evidence for acute health effects comes from studies outside the UK. *Population based studies, especially longitudinal studies in urban and rural environments, should be undertaken as a priority in the UK;* most studies to date have been conducted in the USA.

It is certainly not known whether or not PM_{10} is causally associated with adverse health effects in the UK and this has to be considered a first priority for research. *Epidemiological studies are required to evaluate the acute health effects of small particles (PM_{10} , $PM_{2.5}$**,— particle composition and size distribution to*

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* FEV_1: the volume of air expired during the first second of a maximal or 'forced' expiration. PEF: peak expiratory flow

** $PM_{2.5}$: fine particles with an aerodynamic diameter equal to or below 2.5 µm

be investigated), and oxidant pollutants, O_3 and nitrogen dioxide (NO_2), at current ambient levels in the UK, using a variety of health outcomes. Mixed ecological studies may be useful since they look not only across time at a number of populations but they also look at effects over time in each of the populations studied.

An important question to answer is whether current or projected levels of air pollution are associated with chronic damage to the lung. Measuring chronic (or remote) effects, such as a more rapid decline in lung function with age or increased susceptibility to respiratory infections, is more difficult than measuring acute effects following short-term exposure. Chronic effects can arise following either short- or long-term exposure to air pollutants. The timing of exposure may be very important. For example exposure during childhood is possibly more important than at other times; children have a higher metabolic rate than adults and their lungs are developing. Another uncertainty is whether disadvantage (such as socioeconomic disadvantage) that occurs in early life still has any effect in adult life. These are all arguments in favour of using the cohort study approach, however this is expensive and takes time to produce usable results.

Chronic effects have been investigated by prevalence and by cohort studies. The large US Six Cities study allowed both a cross-sectional and a longitudinal analysis. Although this study was of major importance to our understanding of the effects of particulate pollution, there are problems in the interpretation when a limited number of locations are the basis of the analysis. It is possible that the UK has a better basis from the national birth cohorts to undertake this kind of study than does the USA.

The strengths of cohort studies are that they allow better measures of exposure, of potential confounders and of disease incidence. To be successful, cohort studies need to investigate wide variations in exposures and therefore need to be carried out in a number of locations. This and the length of time required to establish differences in lung growth, or decline in lung function, makes them expensive. In spite of their considerable advantages, there are some unresolved problems in the design of such studies. These include the need for adequate methods to adjust for poorly defined confounders such as foetal nutrition and social class.

The possibility of using The Health Survey for England (Office of Population Censuses and Surveys, 1994), which comprises a series of independent cross-sectional surveys to monitor aspects of the health of the English population, as

the basis for such a study, was discussed. However, these surveys cover only a small number of people (about 5000) spread nationally with no prospect of monitoring pollution or disease on an individual basis. If an association were to be found in such a survey it would need to be followed up with more stringent epidemiological and experimental studies. It was noted that the Department of Health is currently considering proposals for the next such survey and that asthma is a high priority area.

There are many types of time-series data sets such as daily deaths, general practitioners (GP) consultations and hospital admissions already available that could be further exploited. *It is important to ensure that the collection of these data is continued and that the data are preserved.* It was noted that the current Department of Health data sets are run by the Health Regions and that these Regions are about to disappear which may lead to similar loss of data to that experienced in the 1980s. There are also problems because of the data registration acts and some data have already been destroyed.

In the discussion of future epidemiological approaches towards the problem of air pollution and respiratory disease in the UK, it was agreed that a long-term multicentre cohort study was of high priority. Such a study would need to address the questions of fine particulate exposure (size, range and composition), interactions with other components of the pollution mixture, allergens, climate and other social and environmental factors. The predictions are that air quality will change considerably in the UK over the next few decades. Advantage should be taken of this opportunity to study the consequences of changing air pollution levels on health.

INTERACTIONS, CONFOUNDERS AND MODIFIERS

Epidemiological studies can be used to investigate the interaction of air pollutants with other causes of respiratory morbidity and mortality; each cause may have a modifying effect on other possible causes. For example, air pollution might increase the magnitude of an allergic response in an already sensitised person or it might increase the risk of sensitisation in an individual with a genetic predisposition. Air pollution, by damaging the airway epithelium and altering macrophage response, might render the individual more sensitive to viral infections. In infants it is difficult to distinguish virally induced wheezing episodes from asthma; a high percentage of asthma attacks in very young children are triggered by viral infections. The influence of nutrition on the effects of air pollution on the lung has been raised recently. There is current interest in the effects

of dietary antioxidants on respiratory tract defences to oxidant pollutants (Menzel, 1993).

Acute or chronic health effects may be caused by interactions between different environmental pollutants and other factors. *Any study that is set up to investigate respiratory disease should look at air pollution as well as other factors that might influence the disease.* Both epidemiological (e.g. panel) studies and experimental (e.g. controlled chamber) studies are required to investigate interactions between pollutants and other environmental factors such as weather, pollen, viral infections, allergies etc., in the aetiology and exacerbation of respiratory disease. *The possible role of NO_2 and O_3 in increasing susceptibility to infections and allergens should be investigated.*

Data are accumulating on air pollution and asthma, however it is important to be aware of confounding effects in any epidemiological study. Weather is an important confounder in the sense that meteorological conditions affect health. The statistical methods used to control for effects likely to be attributable to weather conditions have been improved but may not yet be adequate. For example, they may control for temperature but not chill factor, or there may be lifestyle factors associated with weather that may have some effect. There are a number of contentious statistical issues, particularly with respect to time-series studies.

In the UK, cold spells during the winter months have a large and not wholly understood effect on day-to-day changes in mortality, notably among the elderly. Since, in urban areas, concentrations of particulates and of some other air pollutants tend to be higher in such conditions there are risks of confounding pollution and weather effects. This problem is sometimes tackled by comparing events in major urban centres with those in adjacent areas where the weather may be similar but air pollution less.

MARKERS OF HEALTH OUTCOME

An important issue is what markers of health outcome should be used to measure the effects of air pollution on health. There are a number of indices of outcome that can be used to measure health effects. Mortality is one such measure and, it is important to know who is dying, for example, the elderly, or asthmatics or people with other severe lung problems. Other measures of outcome are numbers of hospital admissions and GP visits. These may be influenced by many factors

other than health although if such indices are compared over time they are probably more relevant than if compared across geographic regions. Lung function tests have been used in numerous epidemiological studies of environmental and occupational air pollution and a large amount of effort has been put into standardising their administration and interpretation of the results obtained. There is also considerable experience in interpreting the effects of size, sex and age on the results. Similarly, tests of bronchial reactivity are becoming standardised and more widely used in population studies. The number of separate indices that are generated by these tests does, however, produce problems in data handling and interpretation and these physiological changes may not be sensitive enough to show early adverse changes at a tissue level. Bronchial lavage and biopsy are now becoming accepted techniques for investigating early inflammatory and/or oxidative changes at a cellular, biochemical and molecular level. These techniques used in conjunction with chamber studies may allow research workers to establish mechanisms for interactions between pollutants at the target tissue.

There is a need to define the relationship between reactive physiological responses to, for example, oxidative stress and early toxic damage giving rise to cellular inflammatory changes. There may well be different dose-response curves for early reversible physiological responses, for early inflammatory changes and self-sustaining inflammatory disease. The slope and position of these curves would be expected to be different in those subgroups with inherently different susceptibilities. Both population and chamber studies would be needed to define these dose-response relationships.

ASTHMA

One of the central questions about air pollution and respiratory disease is whether air pollution is contributing to the induction of asthma and increasing its incidence and if so whether conditions currently seen in the UK might be causally associated with the disease. Questions should be asked concerning the effects of air pollution on the induction of sensitisation (allergy) and asthma, the incitement of acute asthmatic episodes, the intensity, frequency and severity of asthmatic episodes and on prognosis. If it is important, general air pollution from industrial or vehicular sources will be a contributing cause working with other environmental factors and elements such as individual susceptibility, which may include genetic susceptibility. The evidence for induction is weaker than for incitement but these effects are difficult to investigate. It has been

suggested that increases in air pollution cannot explain the major increases in prevalence of asthma, eczema and hayfever in children which have more than doubled over the past 20–30 years and that one explanation might be that the susceptibility of the population as a whole has increased (Seaton *et al.*, 1994).

There is a need for a range of epidemiological studies to establish the relationship between air pollution in the UK and the incidence and prevalence of asthma, and the precipitation of asthma attacks. The causal factors in this country may be different from elsewhere due to differences in living conditions, climate, vegetation, agricultural practices, transport and diet. Interesting differences in the prevalence of different forms of respiratory disease with different patterns of pollution have been reported in Germany (von Mutius *et al.*, 1992; Nowak *et al.*, 1994). Panel studies, time-series and human exposure chamber investigations may well need to be supported by experimental studies such as the manipulation of antioxidant status in animals to establish the complex relationships between inducing and inciting factors and those affecting susceptibility.

SUSCEPTIBLE POPULATIONS

More information is needed to identify the groups that may be at particularly high risk, particularly during high pollution episodes. For instance it is thought by some that children may be more at risk; there is evidence that, as in adults, their lung function falls during pollution episodes, but it is not established that this actually has any lasting effect. Other groups considered to be at risk include people with chronic obstructive pulmonary disease (COPD), asthma, other forms of respiratory disease and the elderly. It may be that people who exercise during air pollution episodes are at extra risk. It is true that they may experience a decrement in lung function, but it is not clear that this is clinically significant. Smoking is also associated with an increased risk and poor nutritional status may have some effect.

In the general population any adverse effect of air pollution may be difficult to detect except in sensitive subgroups. It might therefore be appropriate to select individuals from ‘at risk’ populations for detailed challenge studies in chambers. Susceptible groups are the primary concern and a case can be made to direct studies towards them. *It is important to identify any groups who are particularly susceptible to air pollution at lower doses than ‘normal’ individuals. Both epidemiological and experimental studies should be undertaken to evaluate more fully the acute and chronic effects in potentially susceptible subgroups. The role of genetic*

differences in mediating the effects of air pollution should also be evaluated.

Not enough is known about variations in susceptibility of individuals to any of the major air pollutants. If there has been a change in susceptibility to air pollution this could arise either due to a small change in the sensitivity of the whole population or to a few individuals who have changed considerably. It was noted that the general population may also include undefined subgroups that are particularly susceptible to different insults. Identification of susceptible subgroups is important for setting air quality standards in that if susceptible subgroups are protected then the healthy population is automatically protected.

Any health effect that might be seen in the general population would have to be addressed vigorously since the number affected would make it an important problem. For example the apparent short-term increase in mortality with an increase in air pollution is of concern if it is a real effect, although it is less important if it is only advancing the death of the already severely ill by a few days. People may be more susceptible because they are on the 'clinical brink'. For example, someone with asthma or chronic cardiorespiratory disease, has reduced respiratory reserves and is therefore more susceptible to a pollution episode.

CONTROLLED CHAMBER STUDIES

Controlled chamber studies can play an important role in studying interactions between pollutants and also toxicological mechanisms. *There is however a lack of such a facility currently being used for this purpose in the UK and the possibility of developing one should be explored.* Chamber studies are expensive but so are large scale epidemiological studies. Although the development of a controlled chamber facility would represent a considerable investment in terms of time and money, many of the research questions identified elsewhere in this report would benefit from such studies with both normal volunteers and those from susceptible subgroups. It is difficult to model what is happening in various subgroups in the population using only animal studies and chamber studies are an important adjunct. *Chamber studies are needed to investigate early adaptive responses to air pollutants as well as other acute responses such as short-term decrements in lung function.*

Chamber studies should be used to identify surrogate markers of inflammation. They could also be conducted using high risk groups; there is little published

literature on the response of highly reactive asthmatics to certain air pollutants. Pulmonary function is not the only valid outcome. The molecular and cellular response of the bronchial epithelium to ambient pollutant levels need to be better understood. There is a need for more appropriate markers of inflammatory response to air pollutants both in 'normal' subjects and in individuals at risk. *Chamber studies could be used to address the issue of susceptibility to allergens and viruses.* It has been suggested that in the presence of inhaled pollutants the lower respiratory tract does become more susceptible to virus infections.

MECHANISMS

The mechanisms involved in the toxicology of the adverse effects of exposure to air pollution need urgent clarification. Studies in experimental animals, chamber studies in volunteers and detailed laboratory investigations of patients with respiratory disease will all be required. The effects of such modifiers as antioxidant status and drug interactions will also require investigation. Findings from accidental exposures to high levels of individual pollutants can be of importance.

There are large interspecies differences in the response of the lung to air pollutants and human studies should therefore be undertaken. Questions to be asked include:

1. What do air pollutants do to the normal lung?
2. What do air pollutants do to the lungs of members of potentially more susceptible subgroups?
3. What are the possible protective effects of antioxidants or other factors?

Such studies need to be carried out in humans since there are uncertainties in extrapolating from animals to humans. Once mechanisms have been identified in humans then it may be useful to utilise animal models for further study. Animal studies therefore need to be closely integrated with human studies. Modern molecular techniques should be used, taking advantage of recent advances in the understanding of the complexity of lung inflammatory reactions at a cellular level.

The toxicology of current small airborne particles (measured for examples as PM_{10} or $PM_{2.5}$) is not well understood. For example, it is not clear how the lung deals with fine particulates, nor is it understood what effects such particles have

on the immune system or the respiratory epithelium. *As well as developing toxicological models for fine particulate exposure more mechanistic studies should be undertaken on oxidant air pollutants such as O_3 and NO_2*

THE POLLUTANTS

IDENTIFICATION AND CHARACTERISATION OF POLLUTANTS

It is important to identify which pollutants are responsible on their own or in combination for any adverse health effects; this is a key requirement when trying to design strategies to reduce risk. Experimental approaches to investigate the effects of air pollutants differ. One possibility is to use the actual type of pollutant mixture of interest. For example, it is possible to study diesel exhausts in a chamber as long as the levels of dangerously toxic pollutants are sufficiently reduced. There is a need to address the real issues of concern such as the air pollutants actually found in the environment, although it is recognised that the exact mixture and its temporal variations are impossible to replicate in chamber studies.

Currently small particles are attracting the most attention as a possible causal agent for the adverse health effects of air pollution. The evidence that exposure to NO_x, at levels likely to occur in the UK, produces a significant effect in normal individuals is weak. Airways hyper-responsiveness can be induced by O_3, and SO_2 can cause narrowing of the airways in individuals with hyper-responsive airways.

More chamber studies of repeated short-term exposures to air pollutants should be undertaken, as these may be helpful in studying acute affects. Large differences have been observed between findings in chamber studies and effects seen during short-term episodes of air pollution. These differences may be very informative. For example, in several studies no change in lung function has been observed in either asthmatic or 'normal' subjects exposed to NO_2 concentrations up to 7500 μg m^{-3} (4000 ppb) in a chamber (Advisory Group on the Medical Aspects of Air Pollution Episodes, 1993). This implies that the changes in lung

function observed in asthmatics during high pollution episodes are probably not due to NO_2 alone.

There is a particular need for more information concerning the chemical and physical nature of the particulate fraction known as PM_{10} (see also next section); the variability of this fraction and for example, the different effects that particles might have if inhaled with acid aerosols of varying pH are poorly understood. The characteristics of particles vary with time and place. *Particular components such as acid aerosols should be investigated and data are needed on airborne particles in the UK atmosphere.*

The main ambient (outdoor) air pollutants under consideration at the present time, for non-cancer health effects, are NO_x, PM_{10}, O_3 and SO_2. It is not known if others are likely to be important; furthermore it is possible that the pollutants currently being measured are not the most appropriate.

PARTICULATES

There is much evidence that particulate pollution, and especially changes in the levels of fine particulates are associated with changes in short-term indicators of respiratory health, including physiological measurements, symptoms, hospital admissions, clinic attendances and mortality. However, most of this work has taken place in the USA and therefore under very different conditions from the UK and there are a number of unanswered questions. Relatively little is known about the size and nature of the effects of fine particles and their interaction with SO_2, NO_x or O_3 at current exposure levels in the UK, or the importance of particle size fractions or their composition for various health outcomes. Particles of the same size as those now measured as PM_{10} existed in earlier pollution mixtures. The old coal smoke comprised particles that were generally even less than 1 μm in diameter.

The effects of suspended particulates, in terms of day-to-day changes in mortality or morbidity being reported currently, are larger than would be anticipated by extrapolation either from the effects of the massive exposures to coal smoke experienced in London up to the 1960s or from studies on occupational exposures to (relatively coarse) dusts in coal mines or other industries. This implies that the 'newer' mix of pollutants, consisting mainly of very fine particles, is more harmful weight for weight than former pollutant mixtures or general industrial dusts. Whether this is related to chemical composition, with such features as

acid/sulphate components now representing a greater proportion of the total particulates, or to physical form with material such as diesel smoke being present as very fine particles having extremely large surface areas in relation to their mass, on which other pollutants may be absorbed, is unclear.

Other factors that may have contributed to the detection of adverse effects even at today's much-reduced concentrations of particulates and associated pollutants include the use of more sensitive markers of effects on health such as GP attendances or hospital admissions for asthmatic conditions and changes in lung function among sensitive groups. More powerful statistical models, often now based on the Poisson distribution (Schwartz & Dockery, 1992) have also been developed.

Because of the major contribution of diesel fumes to the fine particulate fraction in urban areas and the current epidemiological interest in this fraction, more work is needed to characterise diesel particulates.

The origins of PM_{10} in a given location should be identified.

The indoor environment must also be considered. For smaller particles the indoor concentration is typically about 70% that of the outdoor concentration, but this is very variable and depends on many factors including indoor sources and ventilation. Sources of particles indoors include smoking, furnishings and fabrics, and combustion appliances (e.g. fuel burning stoves). Biological particles also make an important contribution to total particulates and differ in origin indoors and outdoors. The sources of biological particles indoors are predominantly bacteria, moulds and dust mites, whereas pollen grains may be of most importance outdoors.

Current knowledge about particles and their effects on health is limited. For example, it is assumed that soluble particles can gain access to the alveoli and interstitial spaces, but the adverse health consequences and the modes of action have not yet been established. Carbon particles have a large surface area and may carry a significant amount of adsorbed material including potentially carcinogenic organic compounds. The role, if any, of inorganic particles such as silica and fibrous minerals at current ambient levels is not known with any degree of certainty.

There is some difficulty in explaining the various adverse health effects that have been found in relation to differing exposures to PM_{10} in terms of current under-

standing of the toxicology of fine particulates. Better understanding will come from a more detailed characterisation of the physical structure and chemical composition of the fine particulate fractions and from toxicological studies of known fine particulate mixtures.

INDOOR AIR POLLUTION

Although current interest has emphasised the possible adverse effects of outdoor air pollution it is recognised that indoor air pollution is probably also of critical importance. Currently indoor and outdoor environments are much more separated than was the case in the past, and due to increased insulation and energy concerns there are currently fewer changes per hour of indoor air than there used to be.

The indoor exposures of most concern with respect to non-cancer respiratory disease are carbon monoxide, NO_2, biological particulates, including allergens (e.g. house dust mites), volatile organic compounds, aldehydes and environmental tobacco smoke. An important issue with respect to indoor air pollution is the role it plays in early life. Babies may be sensitised by events relating to the home indoor environment, and it is particularly important to take into account the role of allergens when considering indoor air pollution.

METHODOLOGICAL ISSUES

EXPOSURE MONITORING

Establishing any relationship between air pollution and health depends on a good knowledge of the type and distribution of pollutants, both in the outdoor and indoor environments, and an understanding of how these change with time. The number of air pollutants and the complexity of the chemistry of air pollution mixtures makes this a difficult sampling and analytical exercise. There are, however, several key issues that need to be considered.

Pollution monitoring stations should be at relevant sites (urban and rural) and at an appropriate position in relation to the polluting source. Although historically more rural measurements of O_3 have been made than urban ones, this is no longer the case. *There should be more suburban as well as central urban monitoring, especially for O_3 and NO_x.* The two monitoring stations in Birmingham (suburban and central urban), for example, correlate well with each other and *this homogeneity of exposure over large urban and rural areas needs to be confirmed elsewhere.*

It is now possible to predict episodes of high air pollution and it would be helpful to carry out more monitoring than usual at such times.

At present the same pollutants are not necessarily being measured in the same way. *The different monitoring methodologies should be evaluated to ensure quality control and harmonisation of output*. Better harmonisation of output will mean the data collected in different studies and locations can be analysed together.

It is extremely important to develop technology for establishing an individual's exposure to pollutants, alone and in combination, over 24-hour periods. There is a need for studies focused on personal exposures, in order to give the typical spread of exposures for individuals and also to find the extremes. Current air pollution monitoring in the UK does not give a detailed picture of an individual's personal exposure. Better long-term, personal exposure measurements are still made using individual (personal) monitoring than using fixed-site monitors; this is certainly the case occupationally. Biological monitoring, however, gives the best measure-

ment of exposure. The use of personal monitoring is only just being introduced for population studies. However, personal monitoring may not always be necessary in order to evaluate personal exposure. The use of monitors, for example, by roadsides or classrooms, together with an integrating formula may be sufficient in some instances. A combination of personal monitoring (especially for extreme exposures), monitoring of microenvironments, and algorithms to predict exposure based on microenvironments and behaviour patterns, may be used to obtain an accurate picture of personal exposure.

Clearly there is a need to know how valid different forms of exposure monitoring are as a measure of individual and population dose. Accurate methods for measuring personal pollution exposure need to be developed and assessed in comparison with fixed-site monitoring. Exposure should be measured in an appropriate fashion with respect to the outcomes to be assessed. Personal monitors could be used to validate other monitoring procedures which may then be sufficient for a given study. Personal monitoring may be of particular use for NO_2 where there may be large variations between different monitoring sites.

It is possible to integrate exposure monitoring with monitoring for biological effects and absorption of individual pollutants, and this might be carried out, for example, in the classroom situation. However some concern was expressed at the Workshop about the practicalities and ethics of the use of invasive procedures such as blood sampling in epidemiological or environmental monitoring studies.

It was recognised that exposure monitoring should be carried out in such a way as to be as relevant as possible for use in epidemiological studies.

In order to address the question 'Who is exposed to what and when?' *further observational studies, personal sampling, the study of susceptible groups, and the comparison of indoor* versus *outdoor exposures were advocated. Sampling strategies are needed that reflect personal exposure and provide controls.*

CHARACTERISATION OF EXPOSURE

Many of the larger epidemiological studies attempt to relate changes in morbidity and mortality to average levels of air pollution in specific geographical areas whereas other studies investigate short-term changes in pollutant concentrations. It is not clear whether changes in health status are related more to:

(i) the average background concentration of a pollutant in a specific area

(ii) the amplitude of short-term changes in the concentration, or

(iii) the rate of change in concentration

The relative importance of each of these may vary from pollutant to pollutant, with different clinical end-points and with the prevailing level of pollution. In an area of high pollution, the average concentration may be the major influence on morbidity and mortality, while in relatively 'clean' areas the amplitude and rate of change may be the major influences. Identification of the relative importance of the levels and changes in pollutant levels may give important insights into mechanisms and the values of different control strategies. *The need to establish the relative importance of these factors should be kept in mind when studies are designed to answer other questions. Thus investigators of short-term pollution episodes, longer term morbidity and mortality studies, monitoring programmes and chamber studies should consider these issues at an early stage.*

INTERVENTION

Although it is desirable to reduce air pollution in general, interventions may be considered at several levels. These may involve information and advice to vulnerable groups or, at a different level, dietary modification to enhance antioxidant defences. Interventions involving dietary or pharmacological means require good empirical justifications. *However any intervention, even the provision of advice, should be formally evaluated. This is clearly an important area of investigation.*

REFERENCES

Advisory Group on the Medical Aspects of Air Pollution Episodes (1991) *First report: Ozone*, London, Department of Health, HMSO

Advisory Group on the Medical Aspects of Air Pollution Episodes (1992) *Second report: Sulphur dioxide, acid aerosols and particulates*, London, Department of Health, HMSO

Advisory Group on the Medical Aspects of Air Pollution Episodes (1993) *Third report: Oxides of nitrogen*, London, Department of Health, HMSO

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G. & Speizer, F.E. (1993) An association between air pollution and mortality in six U.S. cities. *New Engl. J. Med., 329*, 1753-1759

Expert Panel on Air Quality Standards (1994a) *Benzene*, London, Department of the Environment, HMSO

Expert Panel on Air Quality Standards (1994b) *Ozone*, London, Department of the Environment, HMSO

Menzel, D.B. (1993) Antioxidant vitamins and prevention of lung disease. *Annals New York Academy of Sciences, 669*, 141-155

Nowak, D., Jörres, R. & Magnussen, H. (1994) Luftverschmutzung - Asthma - Atemwegsallergien. *Deutsches Arzteblatt, 91*, 38-44

Office of Population Censuses and Surveys (1994) *Health Survey for England 1992. A survey carried out by the Social Survey Division of OPCS on behalf of the Department of Health*, London, HMSO

Quality of Urban Air Review Group (1993) *Urban air quality in the United Kingdom*, London, Department of the Environment, Air Quality Division

Schwartz, J. & Dockery, D.W. (1992) Particulate air pollution and daily mortality in Steubenville Ohio. *Am. J. Epidemiol., 135*, 12-19

Seaton, A., Godden, D.J & Brown, K. (1994) Increase in asthma: a more toxic environment or a more susceptible population? *Thorax, 49*, 171-174

von Mutius, E., Fritzsch, C., Weiland, S.K., Röll, G. & Magnussen, H. (1992) Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br. Med. J., 305*, 1395-1399

Walters, S., Griffiths, R.K. & Ayres, J.G. (1994) Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulphur dioxide and smoke. *Thorax, 49*, 133-140

Research priorities

RECOMMENDED RESEARCH PROGRAMME

A number of major issues of concern were identified from the deliberations of the Workshop members. The issues can be divided into three principle groups, two aetiological and one methodological.

The first area of concern is that of acute or proximate effects of exposure to air pollutants. Health outcomes that might be studied under acute effects are death and morbidity, including asthma attacks, infections, GP consultations and hospital admissions.

The second area of concern is that of the long-term consequences of exposures to indoor and / or outdoor air pollutants. The health outcomes that can be studied are the same as above but also include the development of atopy and asthma, the development of other respiratory conditions, and an acceleration in the decline of lung function.

Finally a number of methodological issues need to be addressed; these relate to monitoring, characterisation of pollutants, characterisation of exposures and characterisation of measures of adverse health effects.

These concerns have been formulated into ten areas in need of further research which comprise a proposed comprehensive research programme.

HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS

A. ACUTE EFFECTS OF EXPOSURE TO AIR POLLUTANTS

1a. Are short-term variations in exposure to outdoor air pollutants in the UK associated with changes in acute morbidity and mortality and, if so, what is the magnitude of the effect?

1b. Is long-term exposure to air pollution associated with increased incidences of acute respiratory morbidity and mortality and, if so, what is the magnitude of the effect?

Recent international data suggest that short-term changes in current patterns of pollution may give rise to increased acute morbidity and mortality. The nature of pollution and differences in climatic conditions in the UK are such that it is important to establish whether these data are applicable to conditions occurring in this country.

Epidemiological studies would help in the assessment of the relationship between background levels of pollution and acute respiratory disease.

2. Which outdoor air pollutants acting either singly or in combination or together with other factors are currently responsible for the acute effects of short-term exposures?

It is very important that mixtures should be studied and particular attention should be paid to particulates. Further investigations of PM_{10}, vehicle exhaust, allergens, NO_x and O_3, would be useful.

3. What are the mechanisms that are involved in the toxicology of the acute effects of short-term exposure to air pollutants acting either singly, or in combination or together with other factors, in humans?

Inhalation studies in both humans and experimental animals to investigate not only measurement of lung function but also other early (tissue and immuno-

logical) markers of effect would be of value. The effects of individual pollutants, pollutants in combination and pollutants together with other modifying factors such as changes in antioxidant status need to be studied. Studies of effects in normal subjects, sensitive populations/at risk groups and of the effect of interventions would be helpful.

It is to be hoped that studies of this type might explain differences found between chamber studies and why smaller effects have been seen in chamber studies than in epidemiological studies. This could be due in part to the modifying effect of mixtures and might suggest possible interventions for prevention. Such studies might lead to the development of appropriate animal models in particular to assess the effects of intervention.

B. LONG-TERM CONSEQUENCES OF EXPOSURE TO INDOOR AND/OR OUTDOOR AIR POLLUTANTS

4. Are short-term and/or long-term exposures to indoor or outdoor air pollutants associated with chronic health effects as characterised by increased morbidity and mortality and, if so, what is the magnitude of the effect?

Epidemiological studies from outside the UK such as the Six Cities study in the USA suggest that air pollution may be associated with adverse health effects, and studies are needed to see whether the results are applicable to the types of pollution and climatic conditions seen in the UK.

Appropriate studies might include cross-sectional or ecological studies, historical cohorts, contemporary cohorts, or mixed ecological studies. The opportunity should be taken now to study the health effects of changing levels of air pollutants in the UK (and Europe) over the next few decades.

Studies are needed to identify groups most at risk from air pollution.

It is thought that influences in early childhood may be of particular importance and that there may be periods of particularly enhanced susceptibility.

5. Which indoor and/or outdoor air pollutants acting either singly, or in combination or with other factors, are responsible for chronic health effects?

Although numerous studies have implicated exposure to individual air pollutants, pollutant mixtures, fine particulates and aeroallergens in the development of respiratory disease, there is no clear understanding of which components of current air pollutant mixtures act or interact to produce the various chronic health effects that have been described. It is also not known whether the relevant exposures need to be long-term or whether single or multiple short-term exposures at vulnerable periods (e.g. childhood) may be critical.

The relative roles of indoor and outdoor air pollution and their interaction is a key issue in view of the amount of time individuals spend indoors.

6. What are the mechanisms that are involved in the development of chronic health effects associated with exposure to air pollutants acting either singly, or in combination or together with other factors in humans?

The mechanisms by which gaseous and particulate air pollutants damage the respiratory tract are complex and may well vary with the actual mixture of pollutants involved. Biochemical and ultrastructural damage is probably manifest before observable changes in the usual parameters of lung function. Studies of individual pollutants, pollutants in combination and pollutants together with other potential modifying factors such as change in antioxidant status would be helpful. The effects of specific dietary or therapeutic interventions may give evidence of specific immunological and/or pharmacological mechanisms involved. Sensitive and specific modern molecular and immunological techniques may help to establish the mechanisms of cellular damage involved.

METHODOLOGICAL ISSUES

In addition to the six aetiological questions outlined above the following methodological issues also need to be addressed.

7. The development of methods for personal sampling and an investigation of the relationship between this and fixed-site monitoring

The use of personal sampling in epidemiological investigations should be devel-

oped and the use of exposure surrogates such as questionnaires could be investigated. There is a need for the development of more appropriate equipment such as lightweight, reliable, fast response personal monitors.

8. Further investigations to characterise particulate air pollutants currently occurring in the UK

There is a need to know the chemical composition, size distribution and physical characteristics of the 'fine particulate' fraction of airborne particles and how this relates to the PM_{10} fraction measured in other studies. The extent of variation in particle composition from place to place and the effects of weather are of special interest. Biological particulates and associated airborne antigens require characterisation as does the effect of gaseous pollutants on them. The extent to which diesel particulates contribute to the 'fine particulate' fraction is also of importance.

9. Characterisation of exposure–response relationships

It has been suggested that the health effects of air pollutants may be dependent on (i) background levels of pollutants, (ii) the amplitude of the change of pollutant levels or (iii) the rate of change of pollutant levels. The relative influence of each of these factors may change in different circumstances.

This could be tested using inhalation studies with an appropriate model chemical in experimental animals. Epidemiological studies may be of some help but would be expected to be of limited value because of difficulties in assessing exposure and the effects of confounding.

10. Characterisation of measures of effect

More sensitive and specific indicators of physiological and pathological response to airborne pollutants should be developed using modern molecular techniques. Changes need to be identified as pathological, physiological or adaptive, and their relevance or relationship to an adverse health effect needs to be clarified.

SOME RESEARCH NEEDS IDENTIFIED

During the discussions in the Workshop a number of specific research needs and knowledge gaps were identified. These are all subsumed under the ten research areas included in the comprehensive research programme described in the previous section. For ease of reference, however, the principal specific research needs identified by the participants, which are highlighted in the Workshop report, are also listed below in no order of priority.

AIR POLLUTION EPISODES

There should be a systematic approach to investigating all episodes of air pollution.

Prospective studies of 'at risk' groups should be undertaken during air pollution episodes.

FURTHER EPIDEMIOLOGICAL STUDIES

Population-based studies, especially longitudinal studies in urban and rural environments, should be undertaken as a priority in the UK to investigate the association between air pollution and respiratory disease. A long-term multicentre cohort study should be given a high priority.

Epidemiological studies are needed to evaluate the acute health effects of small particulates and oxidant pollutants, at current ambient levels in the UK, using a variety of health outcomes.

It is important that the collection of time-series data such as daily deaths, GP consultations and hospital admissions should be continued and that the data should be preserved.

INTERACTIONS, CONFOUNDERS AND MODIFIERS

Epidemiological studies need to consider interactions between components of the air pollution mixture, allergens, climate and other environmental and social factors.

Any study set up to investigate respiratory disease in the UK should consider air pollution as well as other factors that might influence the disease.

The possible role of NO_2 and O_3 in increasing susceptibility to infections and allergens should be investigated.

MARKERS OF HEALTH OUTCOME

Further consideration should be given as to what markers of health outcome should be used to measure the effects of air pollution on health.

ASTHMA

There is a need for a range of epidemiological studies to establish the relationship between the incidence and prevalence of asthma, the precipitating factors for asthma attacks and air pollution in the UK.

SUSCEPTIBLE POPULATIONS

It is important to identify groups who are particularly susceptible to air pollution at lower doses than 'normal' individuals.

Epidemiological and experimental studies should be undertaken to evaluate acute and chronic health effects in potentially susceptible subgroups.

The role of genetic differences in mediating the effects of air pollution should be evaluated.

CONTROLLED CHAMBER STUDIES

The possibility of developing chamber facilities in the UK should be explored.

Early adaptive responses to air pollutants and other acute responses such as short-term decrements in lung function should be investigated.

Surrogate markers of inflammation should be identified.

Susceptibility to allergens and viruses should be investigated.

MECHANISMS

Clarification of the mechanisms for the toxic effects of air pollution is required.

Mechanistic studies should be undertaken on the toxicology of fine particulates and oxidant air pollutants.

The effects of modifiers such as antioxidants and drug interactions should be investigated.

Human studies should be undertaken since there is a wide interspecies variation in the toxicology of air pollutants in the lung.

IDENTIFICATION AND CHARACTERISATION OF POLLUTANTS

Which pollutants are responsible on their own or in combination for adverse health effects?

The chemical and physical nature of acid aerosols and gases should be investigated further.

PARTICULATES

More work is needed to characterise diesel particulates.

More information is needed concerning the chemical and physical nature of fine particulates.

The origins of small particulates at a given location should be identified.

EXPOSURE MONITORING

Pollution monitoring stations should be at relevant sites (urban and rural) and at an appropriate position in relation to the polluting source.

More suburban and central urban monitoring sites should be established, especially for O_3 and NO_x.

Additional monitoring should be carried out during high air pollution episodes.

Monitoring methodologies should be evaluated to ensure quality control and harmonisation of output.

Technology should be developed for establishing individual exposure to pollutants, alone and in combination, over 24-hour periods.

The validity of different forms of exposure monitoring to measure individual and population dose should be investigated.

Methods for measuring personal pollution exposure should be assessed in comparison with fixed-site monitoring.

Indoor *versus* outdoor exposures should be compared.

CHARACTERISATION OF EXPOSURE

The relative importance of (i) the average background pollutant concentrations, (ii) the amplitude of short-term concentration changes, and (iii) the rate of change of pollutant concentration should be investigated in relation to adverse health effects.

INTERVENTION

Interventions, including the provision of advice, to alleviate the adverse effects of air pollution should be evaluated.

ANALYSIS OF PREVIOUSLY PUBLISHED RECOMMENDATIONS FOR UK RESEARCH

The outcome of the present report is a proposed comprehensive programme on air pollution encompassing ten broad areas in need of further research. In terms of setting priorities for research this programme needs to be considered as a whole. For the most part it is neither feasible nor appropriate to attempt to rank in order of priority the ten key areas that have been identified. The fact that it is these particular issues that have been selected indicates their importance relative to other issues that were discussed during the Workshop.

Listed in Appendix 1 (p 43) are recommendations made by the committees and groups which have previously addressed the issue of research needs in the area of air pollution and health in the UK. An analysis of how the health-related questions from these more specific recommendations are related to the ten issues in the research programme is provided below. It is expected that any research projects based on one or more of the ten issues would take account of the recommendations listed in Appendix 1 as well as the specific needs identified in the present report.

The Photochemical Oxidants Review Group and QUARG have also made research recommendations; however, these deal predominantly with priorities for exposure monitoring and are therefore not directly relevant to this report which deals with priorities for health effects assessment. Their recommendations are therefore not reproduced in this report, but can be found in the Photochemical Oxidants Review Group (1990, 1993) and Quality of Urban Air Review Group (1993) reports. The QUARG report on '*Urban air quality in the UK*' does recommend that research should be undertaken to assess the effective-

ness of 'helplines' this is also discussed on page 26 of this report.

The recommendations from MAAPE and the MRC Aetiology of Asthma Working Group are more clearly health related. MAAPE has to date made specific recommendations for three pollutants/groups of pollutants (O_3; SO_2, acid aerosols and particulates; and NO_x). Although the recommendations made by these two groups are somewhat more specific than those made in this report most fall within the broader goals outlined in the research programme recommended on pages 31-35. The numbers in parenthesis in the following text refer to the recommendations listed in Appendix 1 (p 43).

MAAPE recognises that little research is currently underway in the UK into the health effects of air pollutants (1, 8, 19), that the UK has lost the lead it once had in this field, (2) and that most recent epidemiological data have originated in the USA (3). The present report also stresses the need for epidemiological studies to be carried out in the UK (p 14).

The need for epidemiological studies on the relationship between ill-health and air pollutants is recognised by MAAPE. For O_3 the initial emphasis would be on short-term effects (7). For SO_2 and particulates, studies are called for on the effects of low levels of these pollutants on the prevalence of respiratory disease (17) and on the relationship between these pollutants and the incidence of asthma attacks (18). For NO_x the need for studies of the effects of episodes of elevated concentrations on public health is recognised (23) as is the need for investigations into the relationship between levels of NO_2 and the incidence of asthma attacks (24) and the effects of long-term exposure to NO_2 on the respiratory health of children (25). All these epidemiological studies would come within Research Programme items 2 and 5 herein on the identification of the pollutants responsible for acute and chronic health effects.

Concerning atopy and asthma, the Aetiology of Asthma Working Group calls for examinations of the importance of tobacco smoke in increasing the risk for these disorders (27), the importance of the nature and timing of allergen exposure with respect to subsequent rates of disease in childhood (28), and how interactions between air pollutants may affect disease induction (30). These studies on atopy and asthma would fall within the remit of Research Programme items 5 and 6 in the present report. Additional recommendations made by the Aetiology of Asthma Working Group are that the importance of respiratory infections in the aetiology of asthma should be investigated (31), as should the

interaction between environmental and genetic factors in the induction of asthma (32). These issues are also discussed in the present report (p 14).

Calls for research into mechanisms of toxicity and studies in experimental animals and in humans are covered by Research Programme items 3 and 6 in the present report. In this field, for O_3 MAAPE calls for research on the biochemical and cellular mechanisms involved in the effects of O_3 on the lung (5) and on the effects of low concentrations of O_3 in asthmatics and non-asthmatics separately (6). With respect to SO_2 and NO_2, MAAPE indicates the need for basic research into the mechanisms of action in the respiratory tract (11, 21), and investigations into the effects of low concentrations in asthmatics (14, 22). MAAPE also calls for an examination of the interaction between body sulphite loads and responses to inhaled SO_2 (12), for studies into the effects of exposure to SO_2, acid aerosols and particulates on allergic responses (15), and for investigations into the interaction between SO_2 and sulphuric acid and between these two pollutants and others such as NO_2 and O_3 (16). MAAPE also notes the paucity of studies on the health effects of nitric oxide (26).

Under research into the mechanisms of toxicity the Aetiology of Asthma Working Group notes the importance of dietary constituents, particularly sodium and antioxidants, in determining the induction and the severity of bronchial asthma (29). Investigation of modifying factors is also reflected in Research Programme items 3 and 6 herein. The same Working Group also indicates some priorities for research in experimental animals into the aetiology of asthma (33-37).

MAAPE calls for improved monitoring and modelling of O_3 levels (4), for systematic measurements of personal exposures to SO_2 (9) and NO_x, and the particular need for monitoring of NO_x indoors (20). These are all exposure monitoring issues that fall under Research Programme item 7 herein. MAAPE also comments that there is little monitoring of acid aerosols in the UK (10); the present report similarly recommends that acid aerosols should be investigated (p 21).

Research Programme item 8 in this report concerns characterisation of particulate pollutants. MAAPE recognises the need for research into the effects of aerosols comprising fine particulates loaded with sulphuric acid and notes that the chemical nature of the carrier may be important in terms of the response (13).

APPENDIX 1: PREVIOUSLY PUBLISHED RECOMMENDATIONS FOR UK RESEARCH ON AIR POLLUTION

THE ADVISORY GROUP ON THE MEDICAL ASPECTS OF AIR POLLUTION EPISODES (MAAPE)

RECOMMENDATIONS FOR FURTHER RESEARCH: OZONE

1. There is currently very little research into the health effects of air pollutants in general, and O_3 in particular, underway in the UK.

2. The UK has lost the lead it once had in the general area of the effects of air pollutants on health.

3. Most of the epidemiological data assessed by the Advisory Group originated in North America where air pollution problems are different from those in the UK.

4. There is a need for an improved network for monitoring O_3 levels in the UK in order to assess human exposures more effectively. In addition, more mobile measuring stations are needed to assess more effectively local variations in exposure levels in highly populated areas. Work is also needed on modelling systems to improve predictions of O_3 levels, with

particular regard for the distribution of areas likely to suffer elevated concentrations.

5. There is a need for more basic research on the biochemical and cellular mechanisms involved in the effects of O_3 on the lung: in particular considering defence mechanisms against O_3, the role of epithelial cells, mechanisms of tolerance, the interrelationship between patterns of exposure and response, the interaction between O_3 and other pollutants, the potential carcinogenicity of O_3.

6. There is a need for further research on the effects of low concentrations of O_3 in man. This should include: investigation of the dose-response curve in a large group of individuals in controlled conditions in the laboratory, examination of the effects of previous exposure: i.e. effects of different background levels of O_3, investigation of the role of reflexes in the response to O_3, investigation of the phenomenon of tolerance — in particular its specificity to O_3, comparison of the effects of exposure to O_3 in asthmatic and non-asthmatic subjects and the comparison of the magnitude of these effects with those produced by exposure to other challenges and interaction with other pollutants, investigation of the effects of asthma treatment on the response to O_3 in ozone-sensitive asthmatics.

7. There is a need for epidemiological studies which should address the possible relationship between exposure to air pollutants in general, and O_3 in particular, on health. The emphasis would necessarily be on acute effects initially, since studies looking at possible chronic effects are much more difficult. Firstly, available data resources that may provide leads on possible acute effects of clinical significance need to be examined. One developing source of data is provided through commercial, computerised GP consultation and prescribing data, allowing a statistical analysis of day-to-day variations in attendances classified into diagnostic groups. There are also hospital in-patient episode data available on a day-to-day basis through the Hospital Episode System. Daily mortality data could also be examined in relation to pollution episodes. Secondly, there is a need for field work to investigate transient acute effects of pollutants in the UK. Because of the lower frequency of episodes as compared with the USA, some summers passing without any of note, opportunities for studies in pre-arranged periods are very limited but the possibility of 'stand-by' arrangements for studies among potentially exposed groups needs to be considered. While there may not be anything completely analogous

with the 'Summer Camp' groups of children that have been studied in the USA, certain schools, holiday or special physical training activities could be looked at.

(from Advisory Group on the Medical Aspects of Air Pollution Epidsodes, 1991)*

RECOMMENDATIONS FOR FURTHER RESEARCH: SULPHUR DIOXIDE, ACID AEROSOLS AND PARTICULATES

8. As was the case regarding O_3, there is currently very little research underway in the UK on the effects of SO_2. This is particularly to be regretted as much of the classic work on SO_2 was undertaken in the UK by the MRC Air Pollution Unit in the period from 1954 to 1981.

9. Although there is a considerable amount of outdoor fixed-point monitoring of SO_2 and particulates, there is no systematic measurement of what levels people are actually exposed to. This may be quite different from the outdoor fixed-point concentrations; absorption on surfaces indoors will generally reduce concentrations, but where there are indoor sources, such as solid fuel fires, enhanced concentrations can sometimes occur.

10. There is virtually no monitoring of acid aerosols in the UK, particularly in large urban areas. The importance of these pollutants may well be questioned, but at present there are no adequate data regarding levels of exposure upon which a judgement of their importance might be based.

11. There is a need for more basic research on the mechanisms of action of SO_2 in the respiratory tract. In particular the possibility that neurogenic inflammation of the smaller airways might be triggered by the action of SO_2 in the upper airways deserves investigation.

12. The interaction between body sulphite loads and responses to inhaled SO_2 should also be examined.

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13. There is a need for basic research into the effects of aerosols comprising fine particulates loaded with sulphuric acid on the lung. The suggestion has been made that the chemical nature of the carrier particulates may be of critical importance to the response generated. If this is so, monitoring of the nature of fine particulates as well as the number of particles present in ambient air may be necessary.

14. There is a need for further laboratory-based investigation of the effects of low concentrations of SO_2 in asthmatics: particularly in those who are sensitive to SO_2. The effects of SO_2 in other groups of patients such as those with COPD should be investigated. Studies to determine whether tolerance to the effects of SO_2 develops and to investigate the longer term effects of SO_2 challenge are also needed.

15. The effects of exposure to SO_2, acid aerosols and particulates on allergic responses need to be studied.

16. Studies on the interactions of SO_2 and sulphuric acid are also needed. The problem of interactions between these pollutants and others, such as NO_2 and O_3, is likely to be complex but needs to be addressed.

17. There is a need for further epidemiological study of the effects of low levels of pollutants including SO_2 and particulates on the prevalence of respiratory disease.

18. In particular, studies of the relationship between levels of pollution and the incidence of attacks of asthma should be examined. Preliminary work in this field has suggested an association. Further work will be necessary to find out whether this association is likely to be causal, and if so, to quantify it. Belfast experiences episodic high levels of SO_2 in winter and an investigation of the health effects of these episodes is recommended.

(from Advisory Group on the Medical Aspects of Air Pollution Episodes, 1992)*

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RECOMMENDATIONS FOR FURTHER RESEARCH: OXIDES OF NITROGEN

19. As was the case with O_3 and SO_2 there is currently very little research under way in the UK on the effects of NO_2.

20. Although there are many fixed outdoor locations where NO_2 is routinely monitored, there is no systematic measurement of the levels to which people are actually exposed. It is recognised that levels of NO_2 indoors may, in some circumstances, exceed those outdoors; the need for personal monitoring of patterns of exposure is perhaps more important in the case of NO_2 than in that of O_3 or SO_2. More information on the profile of NO_2 concentrations indoors is needed.

21. There is a need for basic research into the mechanisms of action of NO_2 on the respiratory tract; in particular, the role of antioxidant defence systems and the effects of NO_2 upon the immune defence system of the lung should be studied.

22. There is a need for further laboratory-based investigation of the effects of low concentrations of NO_2 on asthmatics, particularly those with more severe airway obstruction and increased airway reactivity: these studies must pay particular attention to the methodology used to measure and to assess changes in bronchial reactivity. Additional studies should determine the effects of repeat exposure.

23. There is a need for further study of the effects of episodes of elevated concentrations of NO_2 on the public health. Studies are under way in London and Birmingham, others are needed.

24. Further studies on the possible relationship between levels of NO_2 and the incidence of asthma attacks should be undertaken. Preliminary work in this field has suggested an association. Further work will be necessary to find out whether this association is likely to be causal and, if so, to quantify it. The interaction between NO_2 and allergens should be studied.

25. There is a need for further epidemiological studies of the effects of long-term exposure to NO_2 on the respiratory health of children. The suggestion that NO_2 impairs the immune defence mechanisms of the lung should

be investigated, as should the suggestion that NO_2 exposure increases the vulnerability of children to infection.

26. There are few studies of the health effects of nitric oxide. There is a need for further laboratory-based investigations of this pollutant as a pure gas and also, to reflect environmental exposure, in admixture with NO_2.

(from Advisory Group on the Medical Aspects of Air Pollution Epidsodes, 1993)*

THE MRC COMMITTEE ON TOXIC HAZARDS IN THE ENVIRONMENT AND WORKPLACE (MRC CTHEW) AETIOLOGY OF ASTHMA WORKING GROUP

RESEARCH RECOMMENDATIONS

27. The importance of tobacco smoking in increasing the risk of atopy and asthma in childhood and in adults encountering novel allergen in a new environment including their place of work should be examined.

28. The importance of the nature and timing of allergen exposure in determining subsequent rates of atopy and asthma in childhood should be investigated. This will require the development and application of standardised techniques to identify atopy and asthma and to measure relevant aeroallergen exposure.

29. The importance of dietary constituents, such as dietary sodium and antioxidants, in determining both the induction and severity of bronchial asthma should be studied.

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30. The interaction of environmental pollutants both indoors and outdoors in the induction of atopy and asthma should be examined.

31. The importance of respiratory tract infections, not only as causes of exacerbations of asthma but as potential modifiers of the induction of asthma in childhood exerting either an adjuvant or protective role and of their part in the induction of 'intrinsic' asthma in adult life should be assessed.

32. Increased understanding of the interaction of environmental and genetic factors in the induction of asthma is needed.

PRIORITIES FOR RESEARCH IN EXPERIMENTAL ANIMALS INTO THE AETIOLOGY OF ASTHMA

33. Investigation of the effect of pollutants (including tobacco smoke) on the induction and persistence of IgE antibody production should be undertaken.

34. The concentrations of allergen required for the induction of respiratory sensitisation and for the elicitation of responses in previously sensitised animals should be examined. In addition investigation of the influence of exogenous factors on such dose-response relationships, including the analysis of possible adjuvant effects of pollutants should be carried out.

35. A more exacting identification of proteins and chemicals which have the potential to cause respiratory allergy in man is required.

36. The role of viruses in the induction of asthma should be assessed.

37. The influence of maternal and early life nutritional factors in the development of asthma should be evaluated.

(from MRC CTHEW, 1994)

REFERENCES

Advisory Group on the Medical Aspects of Air Pollution Episodes (1991) *First report: Ozone*, London, Department of Health, HMSO, pp.90, 91

Advisory Group on the Medical Aspects of Air Pollution Episodes (1992) *Second report: Sulphur dioxide, acid aerosols and particulates*, London, Department of Health, HMSO, p.131

Advisory Group on the Medical Aspects of Air Pollution Episodes (1993) *Third report: Oxides of nitrogen*, London, Department of Health, HMSO, p.119

MRC CTHEW (1994) *Environmental determinants of asthma. A report to CTHEW* (submitted for publication)

Photochemical Oxidants Review Group (1990) *Oxides of Nitrogen in the United Kingdom. The Second Report of the United Kingdom Photochemical Oxidants Review Group*, Didcot, AEA Harwell Laboratory, p.79

Photochemical Oxidants Review Group (1993) *Ozone in the United Kingdom. The Third Report of the United Kingdom Photochemical Oxidants Review Group*, Didcot, AEA Harwell Laboratory, pp.113, 114

Quality of Urban Air Review Group (1993) *Urban air qualities in the United Kingdom*, London, Department of the Environment, Air Quality Division, pp.26, 27, 58, 72, 87, 108, 121, 134, 156

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