Air pollution and health

The rising prevalence and morbidity of asthma have made air pollution a cause of increasing concern. A conference on ‘Air Pollution and Health’ was held at the Royal College of Physicians of London on the 31 January 1996 at which the speakers addressed the historical perspective of air pollution, current public and scientific concerns about its role in asthma, and possible mechanisms of toxicity, and highlighted areas of research that should enable the Department of Health to set better air quality standards in the UK.

Setting the scene

Dr Malcolm Green (Royal Brompton Hospital, London) confirmed that air pollution has been recognised as a public health problem for many centuries though it only became a focus of scientific and public interest about 40 years ago when the burning of solid fuel resulted in high levels of black smoke and sulphur dioxide. The London fog of December 1952 claimed over 4,000 lives due to very high levels of sulphur dioxide and black smoke; after this the government introduced the ‘Clean Air Act’ in 1956. Although this resulted in a considerable reduction in the levels of these ‘traditional pollutants’, the rapid increase in motor vehicle traffic has created a new spectrum of air pollutants, such as oxides of nitrogen (NOx), ozone and particulate matter. Dr Green described the seasonal variations in the levels of these pollutants. Outdoors, oxides of nitrogen are predominantly winter pollutants whilst ozone poses a major health problem in the summer. The temperature inversions in high pressure areas lead to high levels of nitrogen dioxide ‘capping’ the lower atmosphere over the cities. Particularly high levels of ozone are encountered during summer in Mexico City, Los Angeles and Athens.

The health effects of air pollutants depend not only on concentration and duration of exposure but also on factors such as the individual’s age, allergic tendency, pre-existing lung disease, genetic factors, exercise, cold air and cigarette smoking. The Departments of Health and of the Environment have proposed a major research initiative to study the health effects of atmospheric pollutants; this will enable the Department of Health to set better air quality standards in the UK.

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The pollutants

Dr Robert Maynard (Department of Health, London) described the chemistry and toxic effects of the new pollutants (ozone, NOx and particulates) which arise mainly from motor vehicles.

Ozone

Ozone is a photochemical oxidant pollutant formed as a result of a series of complex chemical reactions taking place in the atmosphere, involving oxides of nitrogen, sunlight and volatile organic compounds. The key chemical reactions that lead to the formation of ozone are summarised in Table 1. These reactions occur in minutes to a few hours and are normally in chemical equilibrium so that there is no net formation of ozone (‘photostationary state’). An increase in nitrogen dioxide (NO2) levels and sunlight disturbs the steady state and results in the production of more ozone; this arises as a result of the reaction of vehicle exhausts (containing volatile organic compounds) with NO in the atmosphere to produce NO2. The NO2 is then available for further ozone formation. Levels of ozone in urban areas are often lower than in rural areas because NO emitted from exhausts serves to ‘mop up’ ozone in these areas.

Nitrogen dioxide

Nitrogen dioxide is an important indoor and outdoor pollutant. This gas is produced as a result of combustion of fuel at a high temperature. Outdoors, motor vehicle emissions are the main source of this gas. In a pollution episode in December 1991 the level peaked at 400 ppb in London and was associated with considerable respiratory morbidity; in another episode in 1992 peak levels of 250 ppb were recorded in London and Manchester. These levels have to be taken in perspective against peaks of up to 1,000 ppb indoors.

Particulate pollution

Epidemiological studies have shown an association between particles measuring 10 μm,(PM10) in diameter and cardiorespiratory mortality. Emissions from motor vehicles are a major source of particles in the urban air. The introduction of catalytic converters and integrated policies on road traffic should tackle this.
problem of environmental pollution successfully. Currently there are 19 particle monitoring sites in the UK. In London the annual average density is 26–27 µg/m³; in Belfast the annual average is approximately 500 µg/m³ because solid fuel combustion is still the main source of domestic heating in this city. As a consequence the levels of sulphur dioxide are higher in Belfast during winter than in other cities in Britain.

Petrol and benzene

David Coggon (MRC Environmental Epidemiology Unit, University of Southampton) spoke about the health effects of benzene and petrol. Benzene is a volatile organic compound formed as a result of incomplete combustion of petrol and diesel in motor vehicles. Outdoors, motor vehicle exhausts are a major source of this pollutant, but it is still unclear how high is our exposure to benzene and what risks are associated with this exposure. Indoors, benzene is encountered in the printing, paint, rubber and shoe industries where it is used as a solvent. Benzene is also used in the petrochemical industry in the manufacture of other chemicals such as ethyl benzene, styrene, phenol, cyclohexane and aniline. Relatively high levels are also encountered in dense traffic and filling stations. Personal exposure depends on the concentration and time and on personal habits such as cigarette smoking (passive and active).

Health effects of benzene

Benzene exposure is associated with acute and chronic neurotoxicity, dermatitis, death from cardiac arrhythmia (one report) and bone marrow suppression. Chronic exposure is associated with multiple myeloma, and acute non-lymphoblastic, myeloid and monocytic leukaemias. The results from the epidemiological studies have to be interpreted with caution because of the small number of cases reported, confounding factors, poor estimates of exposure and because relatively little is known about mechanisms and kinetics.

The way forward

Further studies are needed to investigate the mechanisms by which benzene may induce leukaemia, but are not of the highest priority because leukaemia is a rare disease and it is unlikely that many cases are due to motor traffic. Additional measures are needed to keep the levels of benzene as low as possible.

Assessing exposure

Michael Ashmore (Centre for Environmental Technology, Imperial College of Science, Technology and Medicine) described how the assessment of exposure to a given pollutant can be monitored in two ways:

1. Direct approach: This involves monitoring personal exposure or measuring biological markers. This is the best form of exposure assessment because it is the most accurate; however, it is time-consuming, expensive and impractical for assessing populations. We still do not have the technology to measure the spikes in a given period of exposure.

2. Indirect approach: This is based on monitoring stations, also called ‘fixed site monitoring’. The assessment of exposure is based on computer models integrating concentration measurements over a given period with activity data from diary cards maintained by volunteers. Epidemiological studies have suggested that this is not a reliable way to assess exposure and study the health effects because the results vary with the averaging time. In addition, the exposure for a given individual largely depends on his or her daily activities and fixed site monitoring does not measure the cumulative exposure of an individual.

Pollution at work

Professor A. Newman Taylor (National Heart and Lung Institute, London) provided a broad overview of pollutants related to occupational exposure and their chronic health effects. The main agents responsible for occupation-related lung diseases are coal and silica dust causing pneumoconiosis, organic dusts causing extrinsic allergic alveolitis; asbestos causing asbestosis, mesothelioma and lung cancer; and sulphur dioxide, ammonia, chloride and cadmium which cause acute inflammatory lung diseases.

Studying the role of these agents in disease offers a unique opportunity to relate exposure to specific agents and the development of a particular disease. It also provides the opportunity to investigate how personal habits can interact with exposure to disease-producing agents to amplify the risk; for example, cigarette smoking by a subject exposed to asbestos increases the risk of asbestosis five-fold and of bronchogenic carcinoma eleven-fold. Synergism has also been observed in urinary bladder cancer in smokers exposed to polycyclic aromatic hydrocarbons.

Similarly, exposure to industrial detergents increases sensitisation in atopic and non-atopic workers resulting in the development of asthma.

More recently, genetic–environmental interactions have generated considerable interest. Polymorphisms of genes responsible for metabolising carcinogens, eg cytochrome P450, or acetylator status, have been linked to the development of lung cancer. In addition, an association has been shown between certain HLA haplotypes and disease, eg HLA DPB1 and risk of developing berylliosis. These associations are too weak to be useful in identifying those at greatest risk; however, if really strong associations can be identified
several ethical issues, especially in the role of genetic screening in the recruitment of workers, will have to be faced.

Pollution at home

Professor Ross Anderson (St George's Hospital Medical School, London) reviewed recent studies on the health effects of exposure to commonly encountered indoor pollutants. The main pollutants encountered indoors, and their sources, are listed in Table 2. The main factors determining the levels of these indoor pollutants include ventilation, heating and humidity. Among the pollutants of major concern are tobacco smoke, oxides of nitrogen from gas cooking, and moulds.

Tobacco smoke

Tobacco smoke contains a mixture of pollutants including particles, carbon monoxide, oxides of nitrogen, polycyclic aromatic hydrocarbons and nicotine. Important conditions closely linked with tobacco smoking (active or passive) are listed in Table 3. Salivary cotinine is a good indicator of passive exposure to tobacco smoke.

Gas cooking

The levels of oxides of nitrogen and the incidence of wheezing in children are significantly greater in homes where gas cookers are used. A meta-analysis of the main studies related to NO₂ exposure has shown that there is a 20% (odds ratio 1.2) increase in the risk of developing respiratory illnesses amongst children in homes with gas cookers.

Moulds

Epidemiological studies have shown moulds to be a risk factor for wheezing and childhood asthma. These studies have shown that in order to explain the increase in the prevalence of asthma from 10 to 15%, exposure to some risk factors has to increase from 25 to 85%. Since air pollution alone is unlikely to account for this rise Professor Anderson suggested further research on risk factors such as gas cookers, smoking, pets and how these relate to the domestic environment.

Effects in humans

Professor Anthony McMichael (London School of Hygiene and Tropical Medicine) pointed out that although the industrial revolution has been a boon to mankind, it has also brought atmospheric pollution. As the industrial revolution gained momentum, the incidence of respiratory illnesses including chronic bronchitis, emphysema, lung cancer, acute respiratory illnesses, pneumoconiosis and silicosis, has risen dramatically.

The rise in the incidence of lung cancer has mainly been attributed to smoking habits and exposure to carcinogens at work. The carcinogenic effects of air pollution have been overshadowed by the more potent respiratory carcinogens such as cigarette smoke and occupational exposure to known carcinogenic agents. In Poland, 4% of lung cancers in men and 10% in women were attributable to air pollution. Also in Poland, urban residents had a higher incidence of DNA benzyrene adducts in leucocytes than the rural population; similarly, the levels of polycyclic aromatic hydrocarbon DNA adducts were 1.2 times and 1.4 times higher in bus maintenance and railroad workers respectively than in control subjects.

The global incidence of asthma has risen three-fold in the last three decades. Although there has been no strong evidence that air pollution is a causative factor, epidemiological studies have shown a strong link with morbidity. Three different approaches have been used to study the health effects:

- **time series analysis**: Assessing the effects of fluctuations in the levels of pollutants in the atmosphere in a single cross-section of population
- **chronic effects**: Assessing the incidence of illnesses in different groups of population exposed to different levels of pollutants over a period of time
• cohort studies: Obtaining detailed information from sets of healthy individuals followed for a stated period.

Future studies should employ the last approach to get more reliable information.

Pathophysiology

Professor Robert Davies (St Bartholomew's and Royal London School of Medicine and Dentistry) stated that the pathophysiological effects of air pollutants have been studied mainly by exposing volunteers to predetermined concentrations for short periods in an environmental chamber. Most studies have used an exercise protocol during exposures in order to simulate outdoor physical activities. The inflammatory effects have been evaluated using fiberoptic bronchoscopy for bronchoalveolar lavage and bronchial biopsies.

Physiological effects

The physiological effects have been assessed in normal non-smoking volunteers, smokers and asthmatics, mainly following exposure to ozone, sulphur dioxide and nitrogen dioxide. In normal volunteers lung function changes have been demonstrable following exposure to high concentrations of sulphur dioxide; asthmatics seem to be more sensitive to this gas. The responses following exposure to ambient levels of ozone have been evaluated extensively both in normal subjects and in asthmatics. At concentrations greater than 100 ppb, ozone reduces the forced expiratory volumes and rates, inspiratory capacity and total lung capacity, and can induce wheeze, breathlessness and inspiratory chest pain. Following exposure to nitrogen dioxide at similar concentrations the responses are less marked than after ozone or sulphur. Prior exposure to these pollutants can potentiate the responses to inhaled allergen.

Inflammatory effects

Short-term exposure to ozone induces neutrophilic bronchitis in asthmatics and healthy volunteers. This is associated with an increase in interleukin-6 (IL-6), IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the bronchoalveolar lavage. In vitro studies on human bronchial epithelial cell lines have shown an increase in cytokines constitutively expressed by the epithelium, including IL-8, GM-CSF and tumour necrosis factor alpha (TNF-α). In addition, there is an upregulation of leucocyte endothelial adhesion molecules in the microvascular endothelium.

Animals, cells, molecules

Professor Roy Richards (University of Wales College of Medicine, Cardiff) described studies in animals which have provided some valuable clues regarding the role of antioxidants in the respiratory tract lining fluid in protecting the airways from damage. After exposure to oxidant pollutants including ozone, nitrogen dioxide and particulate matter there is rapid consumption of antioxidants including reduced glutathione (GSH), uric acid, ascorbic acid, retinol and α-tocopherol. Once the antioxidant defence is overwhelmed there is tissue injury caused by lipid peroxidation of cell membranes. This results in the release of free radicals which not only cause direct tissue damage but also stimulate the release of inflammatory mediators. Damage to cell membranes activates the arachidonic pathway with the release of proinflammatory substances such as leukotrienes and prostaglandins which also contribute to bronchoconstriction. These studies suggest that dietary antioxidant supplementation may be a useful strategy in protecting 'high risk groups' such as patients with asthma and chronic obstructive airways disease during pollution episodes.

Animal studies have shown that the transition zone between the terminal bronchiole and the alveolus is particularly susceptible to injury following exposure to these pollutants. Chronic exposure (months to a year) to air pollutants such as ozone and particulates induces changes in the lower airways ranging from hyperplasia and metaplasia to fibrosis. Results of studies in animal models should be extrapolated with caution to humans not only because of intra-species variation but also because of 'unrealistic' levels of pollutants used. Nevertheless, they do provide important pointers to mechanisms of pollutant toxicity.

Setting the standards

Dr Richard Derwent (Meteorological Office, Bracknell) highlighted the importance of setting better air quality standards in Europe. There has been no improvement in the air quality in the UK without legislation. Following the December 1991 episode in which there were high levels of nitrogen dioxide, benzene, 1,3 butadiene and carbon monoxide, the government responded by setting up the Expert Panel in Air Quality Standards (EPAQS), launched a programme for more urban monitoring, established the first PM$_{10}$ monitoring station, introduced an air quality bulletin and funded new research into the health impact of air pollution.

The government has set 50 μg/m$^3$ as the daily average concentration for PM$_{10}$. There is a good correlation in winter between PM$_{10}$, NOx and CO, suggesting that most PM$_{10}$ is generated from motor exhausts. EC standards are exceeded most often in winter. In summer PM$_{10}$ levels are closely linked with 'acid rain' resulting from photochemical reactions. The long range transport of sulphate particulates (average life approximately 10 days) from the continent causes
considerable problems in the UK during summer. Although the universal use of lead-free petrol will reduce the number of lead particles in the ambient air, the rapid proliferation of diesel fuelled vehicles will still generate PM$_{10}$ to pollute the atmosphere.

Solutions

Professor Phillip Goodwin (University College, London) looked at ways of preventing some of the problems caused by outdoor pollution. Of the many sources of outdoor atmospheric pollution, motor traffic is the largest. The best way forward is to adopt measures to reduce the number of motor vehicles on the road and also reduce vehicle emissions. Moving from leaded to unleaded petrol will reduce the number of lead particles in the atmosphere. At times when there are unusually high concentrations of pollutants due to bad climatic conditions, local authorities should take measures to impose short-term bans on traffic, especially in city centres. It is still early days for 'pollution free fuels' but with rapid technological advancement this is something we can look forward to.

General comments

This conference brought together the multidisciplinary scientific community working in environmental toxicology to consider the key issues relating to air pollution and health. There was a general consensus that motor vehicle emissions were the largest source of urban outdoor air pollution and that new legislation was urgently needed to reduce motor vehicle traffic in city centres in the UK. Research in environmental toxicology is necessary to develop better monitoring systems for estimating personal exposure, to understand mechanisms by which pollutants exacerbate mucosal inflammation in asthma and to investigate the potential protective role of dietary antioxidant supplementation in asthmatics during pollution episodes.

The speakers largely achieved the difficult task of making their presentations simple, precise and understandable to medical specialists and non-specialists, and to scientists.

Epithelial cell biology—its clinical impact

A conference entitled 'Epithelial cell biology—a science impacting clinically' was held at the Royal College of Physicians of London on 6 March 1996.

Growth control in epithelia

Professor W J Gullick (Royal Postgraduate Medical School, London) gave an overview of the regulation of epithelial growth by positive growth factors and its clinical implications. The combination of a growth factor and its receptor induces changes in the receptor such as dimerisation and phosphorylation which activate second messengers and hence initiate intracellular signals. In pathological states overexpression of growth factor receptors on the cell surface, or mutations of these receptors, can cause unregulated transmembrane signalling independent of ligand binding, driving the cell towards cancerous growth [1]. These receptor abnormalities have a causal role in epithelial carcinogenesis and are not just an epiphenomenon. Growth factor receptor mutations in cancer can be used to indicate prognosis and in future may be used as targets for chemotherapy with monoclonal antibodies.

Dr R Akhurst (University of Glasgow) made the point, using transforming growth factor beta (TGFβ) as an example, that one growth factor can have many different actions on epithelium. At various times TGFβ can act as a potent growth inhibitor, mitogen, stimulator of extracellular matrix production, immunosuppressor, inducer of apoptosis and both a stimulator and inhibitor of differentiation. TGFβ is also implicated in multistage skin carcinogenesis acting at an early stage as a tumour suppressor but at later stage enhances the progression of skin papillomas to carcinomas [2].

Dr G I Evan (Imperial Cancer Research Fund, London) gave an intriguing talk about the control of apoptosis and its relevance to carcinogenesis [3]. There is a dynamic equilibrium between cell proliferation, differentiation with consequent growth arrest, and cell death. Tumour production can arise from deregulation of cell proliferation or inhibition of cell loss. Apoptosis is a rapid, energy dependent form of controlled cell death. The c-myc proto-oncogene encodes for a central component of the cell proliferative machinery and deregulation of c-myc expression is implicated in carcinogenesis [3]. However, it can also

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