National Environment Protection (Ambient Air Quality) Measure

A Review of Existing Health Data on Six Pollutants

Prepared for the National Environment Protection Council by
Dr Jonathan A Streeton FRACP, FCCP, FAFOM

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A suite of documents were prepared for the National Environment Protection Council by various consultants during the development of the National Environment Protection (Ambient Air Quality) Measure. Details of these documents are as follows:

Monitoring & Reporting Protocols - R C Joynt, HRL Technology Pty Ltd

Air Quality Management Options – Pacific Air and Environment

Exposure Assessment – Dr Tom Beer, CSIRO and Sean Walsh, EPA Victoria

A Review of Existing Health Data on Six Air Pollutants – Dr Jonathan A Streeton

Electronic copies of these documents are available from:

National Environment Protection Council Service Corporation
Level 5, 81 Flinders Street
ADELAIDE SA 5000

Telephone: (08) 8419 1200
Facsimile: (08) 8224 0912

These documents are also available online: http://www.nepc.gov.au

TERMS OF REFERENCE

Purpose:

To provide details of the current state of knowledge of the human health effects of the following pollutants:

- carbon monoxide
- lead
- nitrogen dioxide
- photochemical oxidant (as ozone)
- respirable particles
- sulfur dioxide

Tasks:

For each of the listed pollutants

1. Review, evaluate and as necessary provide updates from primary data sources, national and international reviews on the available health related data.

2. Assess the range of impacts (both sub-clinical and clinical) on human health of the general population and that of any susceptible subgroups.

3. Identify the dose response relationship and identify any thresholds for the effects on human health.

4. Recommend the concentration range that would provide protection from the lowest observable adverse effects on susceptible populations.

5. Provide detailed justification and references for these recommendations.

6. Prepare a detailed draft report for consideration by the Health Review Panel.

7. Provide briefing to the Health Review Panel as required.

8. In the light of comments received, submit final report to the NEPC Service Corporation.

> *'…this most excellent canopy, the air, look you, this brave o'erhanging firmament, this majestical roof fretted with golden fire, why, it appears no other thing to me than a foul and pestilent congregation of vapours.'*
>
> Hamlet, II, ii, 318 - 22.

AUTHOR'S DEDICATION:

To my family who have had to once again put up with my preoccupation, irritability, and seemingly never-ending clutter of books and papers.

This review is offered as a tribute to a tireless worker for international pollution control, the mentor of many, David Bates of Vancouver, BC, Canada.

REVIEW TEAM

To undertake this review, a project team was established, the members being as follows:

Dr. Jonathan A. Streeton, MBBS, FRACP, FCCP, FAFOM (Principal Consultant, with responsibility for the whole project, the editing of draft commentaries, the preparation of summary statements, and the review of literature reviews and preparation of commentaries on both carbon monoxide and respirable particles).

Dr. Lynette S. Denison, B Sc(Hons), PhD(Melb) (on secondment from the Victorian EPA for this project, and with responsibility for the preparation of initial literature searches and reviews on the six air pollutants).

Dr. Michael J. Abramson, B Med Sci(Hons), MBBS, PhD(Newc), FRACP, FAFPHM (with responsibility for reviewing the literature review and preparing a commentary on the health effects of nitrogen dioxide).

Dr. Charles S. Guest, MBBS, BA, MPH(Havard), PhD(Melb), FAFPHM (with responsibility for reviewing the literature review and preparing a commentary on the health effects of photochemical oxidants/ozone).

Dr. Guy B. Marks, B Med Sci, MBBS, PhD(Syd), MRCP, FRACP, FAFPHM (with responsibility for reviewing the literature review and preparing a commentary on the health effects of sulfur dioxide).

Professor John J. McNeil, MBBS, FRACP, M.Sc(London), PhD(Melb), FAFPHM (with responsibility for reviewing the literature review and preparing a commentary on the health effects of lead).

Dr. David V. Bates, MD(Cantab), FRCP, FRCPC, FACP, FRSC (with responsibility as an external reviewer for reviewing the draft commentaries and summaries, to advise on recent literature, and to recommend appropriate revisions to guidelines/standards).

Dr. Streeton would like to place on record his sincere thanks for the efforts of his colleagues in completing their assigned tasks with efficiency and good humour, especially in view of the time constraints on the project.

ACKNOWLEDGEMENTS:

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SUMMARY OF RECOMMENDATIONS[*]

CARBON MONOXIDE

Risk Groups:
- those with ischaemic heart disease
- those with other forms of cardiac disease, including cyanotic heart disease
- those with hypoxaemic lung disease
- those with cerebrovascular disease
- those with peripheral vascular disease
- those with anaemias and haemoglobin abnormalities
- children
- the developing foetus

ProtectiveRanges:

A carboxyhaemoglobin level of not more than 2.5% whilst either at rest or during active physical exercise should not be exceeded.

To achieve this level, the following concentrations are recommended for protection of these risk groups:

Eight hour exposure: 10ppm

One hour exposure: 25 - <u>30</u> ppm

30 minute exposure: 50 ppm

15 minute exposure: 90 ppm

LEAD

Risk Groups:
- young children
- developing foetuses
- possibly the adult population (low level of risk)

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Protective Range:

Moving monthly mean average: 0.3 - <u>0.5</u> $\mu g/m^3$ not to be exceeded

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[*] Underlining indicates preferred value

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NITROGEN DIOXIDE

Risk Groups:
- young children
- asthmatics of all ages, but especially children
- adults compromised by chronic cardiac and respiratory disorders

Protective Ranges:

The current LOAEL for NO_2 is in the range of 0.2 - 0.3 ppm, but with an increasing body of data to suggest that longer term chronic indoor exposures to concentrations of 0.04 - 0.08 ppm during early and middle childhood can lead to the development of recurrent upper and lower respiratory symptoms.

One hour averaging period (not to be exceeded):   <u>0.10</u> - 0.15 ppm

but range 0.10-0.12 ppm preferred

Annual averaging period: 0.02 - <u>0.04</u> ppm

OZONE:

Risk Groups:

- those with asthma and chronic lung diseases
- healthy young adults undertaking active outdoor exercise over extended periods
- the elderly, especially those with cardiovascular disease

Protective Ranges:

No threshold exposure levels can be identified for ozone

Primary Standard:

(Six -) to Eight (8) Hour Exposure (on a rolling basis during daylight hours, not to be exceeded):

<u>0.05</u> - 0.06 ppm (50 - 60 ppb)

Secondary Standard:

One (1) Hour Exposure (not to be exceeded):

<u>0.08</u> - 0.09 ppm (<u>80</u> - 90 ppb)

RESPIRABLE PARTICLES

Risk Groups:
- healthy children
- adults with obstructive lung disease
- asthmatics

Protective Ranges:

PM$_{10}$: 24 Hours: 50 µg/m^3

PM$_{2.5}$: 24 hours: <u>20</u> - 25 µg/m^3

No ANNUAL value range is indicated at this time.

Consideration could be given to the later introduction of a guideline/standard based on exposure - response relationships.

SULFUR DIOXIDE

Risk Groups:
- asthmatics
- those with chronic obstructive lung disease

Protective Range:

15 minute exposure: 0.175 ppm (500µg/m^3)

24 Hour exposure: 0.04 ppm (125µg/m^3)

Annual exposure: 0.02 ppm (50µg/m^3)

RESPIRATORY DEFENCES

INTRODUCTION

The human respiratory tract can be divided into two main parts: the upper respiratory tract, which includes eyes (lacrimal ducts), nose, mouth, throat and upper large air passages to the level of the larynx; and the lower respiratory tract, which includes all passages below the larynx from the trachea down to the alveolar membrane (gas exchange membrane).

Each part of the respiratory tract has evolved with its own specific defence mechanisms, and together, under normal conditions, these various defence mechanisms provide adequate protection for the delicate and sensitive alveolar membrane within the lungs across which the exchange of gases - in particular, oxygen and carbon dioxide - takes place between the external air and the blood.

The total surface area of the alveolar membrane in an adult is between 120 and 150 square metres, roughly the size of a tennis court, and it is in fact the only internal organ of the body which is in constant direct contact with the external environment. Each day, an adult, sitting quietly at rest or gently exercising, inhales between 9,000 and 12,000 litres of air pass into the lungs, this volume increasing significantly with moderate exercise or hard work. Besides the mix of gases (both beneficial and harmful) in each litre of inspired air, there are literally millions of particles of different sizes and configurations including bacteria, viruses, fungal spores, pollen grains, asbestos fibres, inorganic dust particles, exhaust fumes, smokes, mists, and organic compounds. The lung membrane has the potential, then, to be injured by a wide range of noxious airborne substances, and the defence mechanisms which protect it are of considerable importance.

The upper airway, including eyes, nose and mouth, is extremely vulnerable to irritant materials and gases, and irritation results in a range of well-recognised effects: burning and watering of eyes, nose and throat; sneezing; over-production of mucus from the para-nasal sinuses and the nasal passages; and the aggravation of underlying allergic tendencies.

THE UPPER RESPIRATORY TRACT

The mouth and more importantly, the nose constitute the main defences in the upper respiratory tract. The nose is a complex organ, richly supplied with blood vessels, a lining mucous layer, a convoluted bony structure, and housing the olfactory sense.

As inspired air passes through the nose, it is warmed and humidified to body temperature; the major bulk of inspired particles is removed, down to a

particle size of the order of 10 μm (microns or micrometres); and harmful substances are detected by their smell, especially those compounds containing traces of sulfur. The mouth also warms, humidifies and filters air, though less efficiently than the nose. By the time inspired air reaches the back of the throat under normal or even moderately extreme climatic conditions, virtually all particles down to 10 μm (PM_{10}) have been cleared.

Recently published research is now demonstrating that the nasal airways appear to be the primary target for at least some of the commonly occurring pollutants, in particular, ozone and respirable particles. There is now evidence that exposure to both of these substances can rapidly lead to reproducible inflammatory changes in specifically susceptible regions of the nasal membranes, both in experimental animals and in human subjects (especially in children). These nasal responses appear to be precursors to similar responses previously identified in the lower respiratory tract.

THE LOWER RESPIRATORY TRACT

Below the larynx, the trachea, the main trunk airway, branches to form two major bronchi, one leading to each lung. Each bronchus then branches some 23-24 times into smaller and smaller airways (the bronchioles) to terminate finally in the alveoli, the tiny sacs where the exchange of gases between the air and the blood actually takes place. Throughout this system there are a number of separate but inter-related defence systems operating, all designed to prevent anything other than pure clean air from reaching the alveolar membrane.

Nerve endings and receptors (cough receptors) line the trachea and the major bronchi. These react to the presence of larger particles and some gases such as sulfur dioxide (SO_2), producing irritable coughing in the attempt to expel the foreign substance. In some people, the frequent irritation of the nerve endings can lead to increased irritability in the muscular walls of the airways, resulting in conditions such as asthma (where the muscle walls go into spasm, narrowing the airways). The situation is further complicated by excessive mucus production from enlarging and over-active mucous glands within the walls of the bronchi and bronchioles.

As the inhaled air moves progressively down the respiratory tract, particles, bacteria and viruses still contained in the air-stream are progressively deposited and trapped on the sticky layer of mucus which covers the airway walls. This mucus is then progressively moved upwards until it reaches the throat and is swallowed or expectorated, and the upwards movement is achieved by the synchronous beating of the cilia, millions of tiny hair-like projections lining the inner surfaces of the air passages. By the time the air reaches the smaller peripheral airways (the bronchioles) all particles down to around 1 μm have been cleared.

The delicate mucus/cilia system is particularly vulnerable to a number of inhaled toxins, irritant gases, and organic compounds, especially tobacco smoke and diesel exhaust, and to the effects of viral and bacterial infections. Under these influences the cilia may beat in a disordered manner, or even to stop beating entirely, and the mucus blanket is no longer adequately cleared

The branching air passages provide another defence mechanism. As already mentioned, the respiratory airways branch some 23 or 24 times between the trachea and the alveolar membrane. At each bifurcation, a zone of turbulence is set up which causes particles, bacteria and gases in the air stream to impinge against the airway walls and, in the case of solids, to adhere to the sticky mucus layer. The particles which collect in the mucus layer are frequently coated with organic materials, including carcinogens (cancer producing substances), and the effectiveness of this mechanism for removing particles is demonstrated by the fact that malignancies or cancers of the lung frequently develop at these bifurcations, where the carcinogens have built up over time. Tobacco smoke is a major source of such carcinogen-coated particles.

Mobile scavengers, the pulmonary alveolar macrophages, move about within the airways. These specialised cells, derived from the blood and lymphatic systems, are able to squeeze out between the lining cells of the alveolar membranes and the air passages. They move freely about the inner surfaces of the alveoli and smaller air passages, where they scavenge very small particles, viruses and bacteria which have penetrated to the depths of the respiratory tract.

Macrophages are immunologically competent. Not only are they able to surround and engulf particles (as an amoeba can be seen to do in a drop of pond water), but they also institute a range of chemical responses or reactions leading to the development of what is known as an inflammatory reaction. Tobacco smoke is a potent activator of macrophages; so are irritant and reactive gases such as ozone (O_3) and nitrogen dioxide (NO_2). If macrophages are persistently activated, they recruit more macrophages to the site of irritation, and a vicious circle of irritation, reaction and increasing inflammation is set in train. Ultimately other chemicals are produced which can cause a number of different end-responses including asthma, bronchitis and allergic sensitisation.

The delicate alveolar membrane lining the alveoli, is very susceptible to direct irritation and injury from inhaled toxic gases such as ozone or nitrogen dioxide. Persistent inflammation results, due to the leakage of proteins, antibodies, white blood cells and other cells into the air space, thus instituting and sustaining a further cycle of damage and injury. The ultimate result of this type of response may be the gradual breakdown of the alveolar membrane itself in the condition known as emphysema.

In some situations a scarring reaction can occur at deeper levels of the alveolar membrane, leading to distortion and destruction of the membrane. This is termed fibrosis, and can result from the inhalation of vastly excessive levels of dust, such as can occur during occupational exposure to silica and asbestos. Other situations which are now being recognised as possible causes of lung fibrosis include prolonged exposure, over years, to irritant gases such as ozone and nitrogen dioxide.

The mucus blanket already described is secreted by specialised cells and glands in the lining of the larger air passages: these are the goblet cells and bronchial mucus glands. The glands can pour out mucus either following irritation, or as a result of reflex nervous stimuli set in motion to counteract irritation caused by inhaled particles and gases. This is one of the hallmarks of the disease process known as chronic bronchitis. Chronic bronchitis is the commonest response to tobacco smoking, and following exposure to excessive amounts of dusts, fumes, irritant vapours and toxic gases, and is characterised by the over-secretion of bronchial mucus leading to constant coughing, the production of excess mucus (sputum) and, where air passages become congested and blocked due to mucus plugging and muscle spasm, by wheezing.

In addition to these various mechanical barriers, there are also a number of complex immunological and chemical defence systems functioning in the respiratory tract, in which various blood and tissue cells play major roles in antibody and chemical responses to foreign substances in the lungs. Increasingly, researchers are recognising the short-term and long-term results of these immunological and chemical reactions, which can exert major effects on body systems remote to the lungs (such as heart and brain), and thereby cause major health effects including long-term disability, and death. As yet, the precise mechanisms whereby these effects are produced have not yet been satisfactorily elucidated (such as the effect of exposure to respirable particles leading to increased mortality (death) rates in those who have underlying heart and lung disease), but the evidence that such effects occur is statistically strong and can be seen in every population group examined thus far around the world.

SUMMARY

The human respiratory tract employs a number of defence mechanisms to protect its inner membranes, and therefore the body as a whole, from the physical and chemical insult which can be caused by inhaled foreign substances and gases. The major defences are, in the upper airways, the nasal and related passages, and in the lower airways, the cough reflex, muco-ciliary clearance, the macrophages, and immunological mechanisms.

Given these defences, we are able to exist comfortably in the normal external environment. It is only when we are exposed to excessive amounts of foreign materials, and these responses are either over-activated or overwhelmed, that increasingly significant inflammatory reactions occur in the respiratory tract. It is these reactions which lead, in the longer term, to more persistent and chronic damage, and to conditions such as asthma, chronic bronchitis, emphysema, susceptibility to chest infections, pneumonia, and lung scarring or fibrosis.

THE NATURE OF AIR POLLUTION

INTRODUCTION

Pollution patterns vary considerably from country to country, and from region to region, with differences in climate, geography, population density and socio-economic conditions having major effects on the resultant patterns of pollution. Europe is commonly regarded as being highly polluted primarily because of its history of heavy particle and sulfur dioxide contamination, although now vehicle exhaust fumes currently predominate leading to varying degrees of photochemical pollution. North America, on the other hand, combines this European-style pollution (especially on the north-eastern seaboard, with a far larger component of photochemically induced gases and aerosols in the western and southern regions. A largely agrarian community in the Third World may also have considerable pollution problems with high indoor levels of smoke from cooking fires (especially dung fires), high particle levels in the dusty atmosphere, and serious food and water contamination, whereas the densely populated urban areas are heavily contaminated by vehicle exhaust fumes and by fugitive particles.

Here in Australia, photochemical pollution predominates the urban areas, but with specific point sources in different parts of the country leading to localised areas of concern.

A brief outline follows of the major types of air pollution which are currently causing concern throughout the world.

SULFUR DIOXIDE AND PARTICLE POLLUTION

Sulfur dioxide and air-borne particles constitute the classic type of air pollution, a form which has been recognised for centuries and which remains, to a greater or lesser extent, the major pollution pattern in the Northern Hemisphere. It results from the combustion of fossil fuels, chiefly coal and oil fuels, which characteristically contain significant quantities of sulfur-containing compounds derived from the original processes of decomposition. On combustion, the sulfur component is normally oxidised to sulfur dioxide gas; or, if the combustion process takes place in an oxygen-reduced atmosphere, other sulfur-containing compounds will be produced, resulting in the production of characteristically unpleasant odours.

The combustion process results also in the production of quantities of ash and soot, mainly in the form of inadequately burnt carbon particles. These particles can then act as nuclei about which water molecules may coalesce. These water molecules may derive from the same combustion source, or may already be in the atmosphere. Airborne sulfur dioxide can then dissolve in

this layer of water to produce a coating of sulfuric acid surrounding these hydrated particles. The end result is an atmosphere heavily laden with a mist or an aerosol of sulfuric acid in association with minute particles.

Sulfuric acid aerosol, however, may form in conjunction with water droplets (clouds) without the presence of air-borne particles. As the cloud evaporates, the droplet residue (in this case sulfuric acid) emerges as an aerosol. In areas affected by photochemical smog, sulfuric acid aerosols can also develop by a process known as 'homogeneous nucleation' whereby gaseous sulfuric acid and water molecules combine to form hydrated sulfuric acid liquid droplets:

$$x H_2SO_4(gas) + y H_2O(gas) \rightarrow (H_2SO_4)_x(H2O)_y(liquid)$$
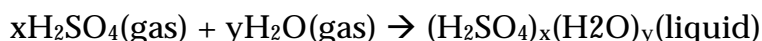
Although this process is more difficult, in thermodynamic terms, than straight condensation on to hydrated particles (the process of condensation does not require excess surface energy), there is good evidence to suggest that homogeneous nucleation is occurring frequently in the atmosphere in a random and ubiquitous manner, and could well be the major source for the well-defined layer of sulfuric acid droplets known to exist at high altitude.

This sulfuric acid aerosol may react with the ammonia which is always present in the atmosphere to form various species of ammonium sulfate particles - NH_4HSO_4 or $(NH_4)_2SO_4$. Evidence would suggest that these particles usually constitute the dominate proportion, by number, of particles present in any air mass, whether clear or polluted, although they may not dominate by mass or weight.

The effects of these aerosols are well documented. They may build up in the air to reach dangerous concentrations, as experienced in the London smogs, resulting in a heavy death toll. More insidiously, they may be washed out of the air and fall as acid rain.

The hydrated particles can also act as carriers for various other substances. Air-borne nitrogen dioxide may dissolve in the surface water to form nitric acid, or the particles may be surrounded by an assortment of combustion products, including a number of carcinogenic compounds such as polycyclic hydrocarbons.

Fortunately, as Australian fossil fuels generally have low sulfur contents, this form of pollution has been minimal in Australia, and has occurred only in relation to specific smelter activities where sulfur dioxide is derived from the burning of sulfide-containing ores rather than from fossil fuels, or adjacent to large oil refineries or chemical installations. Nevertheless, gross local environmental damage has occurred in some places. The devastated landscape surrounding Mount. Lyell and Queenstown in Western Tasmania is a dramatic example of the degree of damage that can be caused by this form of pollution. Serious environmental damage may still be occurring in some Australian localities, although where the pollution source is situated in an

area of very low rainfall, such as Mount. Isa in North Queensland, the effects on the environment may be far removed from the source. In Victoria, studies in Melbourne and the Latrobe Valley have not produced any significant evidence of acid rain.

PHOTOCHEMICAL POLLUTION

Photochemical pollution occurs primarily in urban areas and results from the interaction of several factors, including high local densities of cars, trucks and other mobile combustion sources producing nitrogen oxides (NO_X) in large quantities, plentiful sunlight, an atmosphere contaminated with hydrocarbon compounds, and local climatic factors which tend to concentrate the combustion products in the area rather than dispersing them rapidly (inversion layers, local wind patterns, topography, etc.). This form of pollution presents by far the most significant threat to the air environment in Australia.

A discussion of anything but the basic chemical reactions involved is beyond the scope of this review. In essence, the primary pollutant involved is nitric oxide (NO), which is derived directly from high temperature oxidative combustion processes such as occur in industry, petroleum fuelled cars, and power stations. Whilst nitric oxide has not itself at the present time being identified as a threat to human health, it serves as the basis for the production of secondary and tertiary pollutants such as nitrogen dioxide (NO_2) and ozone (O_3). Other oxides of nitrogen, including nitrogen dioxide, are also directly produced, but in smaller quantities, in combustion reactions.

There are also a number of natural sources of nitrogen oxides, including emissions from soils during, for example, biological nitrification-denitrification processes; nitrogen fixation by lightning; and emissions from naturally occurring biomass burning. These sources vary considerably in proportion and impact. They are unlikely to be of significance in highly polluted urban areas, but may well be of importance in rural areas. To complicate matters, nitrogen oxide emissions from soil can be dramatically increased in agricultural areas through the undisciplined use of nitrogen-containing fertilisers.

Nitrogen oxides and hydrocarbons can accumulate and reach high concentrations, especially where continuous emissions from a stream of motor vehicles are combined with low wind speeds and limited vertical mixing in the meteorological phenomenon known as a 'temperature inversion'. Under the influence of the ultraviolet component of sunlight, complex inter-related chemical reactions occurring over some hours produce a range of secondary compounds.

Among the end-products are some highly reactive and potentially toxic substances; however nitrogen dioxide and ozone predominate, and these two gases are regarded as the best indicators of photochemical pollution. The environmental effects brought about by all these end-products may be compounded by the presence of hydrocarbons, all these elements combining to produce what has become popularly known as 'photochemical smog'. This mixture is chemically quite different from the classical mixture of smoke containing acidic particles and carbon, and fog which had become known as 'smog' by the early years of this century.

In clean rural air (unlike urban air), where the only hydrocarbons present are those naturally produced by vegetation, the photochemical processes that occur involve a series of generally well understood chemical reactions.

The nitric oxide produced by, for example, the morning peak traffic is converted over several hours to nitrogen dioxide. In the presence of sunlight and oxygen, a series of chemical reactions can then take place:

1. $NO_2 + hv \rightarrow NO + O$
   where hv is sunlight energy and O is atomic oxygen.

2. $O + O_2 + M \rightarrow O_3$
   where M is any passive non-reacting substance such as nitrogen or even another oxygen molecule.

3. $NO + O3 \rightarrow NO2 + O$

Thus reactions 1 and 2 lead to the production of ozone, and reaction 3 to its destruction. The net effect of the three reactions in relatively clean air is that the ozone produced is degraded by nitric oxide, whilst nitrogen dioxide is being continually destroyed and regenerated; thus an equilibrium is established along the following lines:

$$\frac{[NO_2]}{[NO]} = k \qquad \text{(more or less constant)}$$

where [ ] indicates the concentration of a chemical species, and k is a constant.

In urban air contaminated by a wide range of reactive hydrocarbon compounds (often referred to as volatile organic compounds or VOC's), however, the reaction patterns are far more complex and less predictable. In the presence of VOC's, an alternative reaction 3 occurs:

Alternate 3. $RO_2 + NO \rightarrow NO_2 + RO^-$
        where RO^- represents any reactive organic compound.

This alternative reaction allows for the regeneration of nitrogen dioxide without the destruction of ozone. The nitrogen dioxide is accumulated during the early part of the process, and as the process repeats itself, there is also a progressive build up in ozone concentrations. Nitric oxide nevertheless remains the destroyer of ozone.

Thus in an air environment containing unburnt fuel, or a volatile hydrocarbon compound from any source (domestic or industrial), the potential exists for the formation of a range of reactive oxidant compounds, particularly aldehydes (RCHO) such as formaldehyde (CH_2O_2), ozone (O_3), peroxyacetyl nitrate (PAN), various hydroxyl (OH^-) and hydroperoxyl (HO_2) radicles, and hydrogen peroxide (H_2O_2).

Other series of complex oxidative reactions can stem from these substances, including the production, by photochemical means, of sulfuric acid (H_2SO_4) and sulfate (SO_4^{2-}) from sulfur dioxide (SO_2), and the conversion of nitrogen oxides to nitric acid (HNO_3) and to nitrates (NO_3^-). Sulfates and nitrates occur as particles, often after interaction with ammonia (NH_3) to produce ammonium salts (NH_4^+), with the accompanying adverse health effects of acidic particles. They also produce visibility reducing atmospheric haze; they lead to acid rain; and they cause damage to vegetation, buildings, textiles and other organic substances.

ACID AEROSOL HAZE

Acid aerosol haze has not yet been demonstrated to be a significant problem in Australia, but in many parts of the Northern Hemisphere, especially in North America, it is being increasingly recognised as a major component of air pollution, and one which can significantly damage human health. In satellite photographs of the USA, acid aerosol clouds can be seen extending far out over the adjacent oceans from the coastlines.

Acid aerosol haze is a combination of classical sulfur dioxide/particle pollution, with photochemical pollution involving nitrogen oxide, ozone and reactive hydrocarbons. The resulting aerosol is generally acidic in nature, and consists of highly reactive photochemical products, nitric and sulfuric acids, and their salts, as droplets or as particles (see above). Where these two forms of pollution are combined, each of the different components (sulfur dioxide, ozone, nitrogen dioxide, acid droplets etc.) enhances the effects of the others on living tissues including the human respiratory tract.

OTHER POLLUTANTS ASSOCIATED WITH COMBUSTION PROCESSES

In addition to the reactions and combustion products already described, a wide range of substances are known to be produced during combustion processes. The actual range of substances produced in any one particular combustion process depends on many factors, including the temperature of the process, the amount of oxygen present, the nature of the substance or fuel being burnt, and various other physical considerations. Some substances such as carbon monoxide, lead and particles can be released in significant quantities to the air environment and have long been recognised as toxic. Other substances, although present in much smaller quantities, have the potential to damage human health in the longer term. Among these are included a large number of reactive organic compounds, many of which have irritant properties (formaldehyde is a good example).

Other combustion products, including many polycyclic aromatic hydrocarbons, may be involved in further photochemical reactions to produce even more reactive compounds, including amines and nitrosamines, many of which are recognised as being carcinogenic (these are also to be found in tobacco smoke), as well as being locally irritant in lung and other organs. When inhaled as particles and deposited in the human respiratory tract, these compounds can result, years later, in the development of malignant tumours in susceptible individuals.

UNCONTROLLED AND CATASTROPHIC EMISSIONS

In recent decades, there has been a steady increase in the range of toxic substances (including proven or potential carcinogens) released to the atmosphere. Some of these releases are impossible to predict, such as chemical spills (accidental or intentional), volcanic eruptions, or major fires, both natural and chemical; and each must be considered on an individual basis.

The majority of these emissions are potentially subject to control, and particular attention needs to be paid to the wide range of chemicals which are routinely emitted by industry. Many of these are hydrocarbons, and are subject to only minimal controls. Whilst each of these emissions may not in themselves constitute a currently recognised health risk, all contribute to the total mass of hydrocarbons in the atmosphere, forming the substrate for the production of large amounts of ozone and other secondary reactive oxidants.

There are, in addition, many significant natural sources of hydrocarbons, including the metabolism of terrestrial plants, bacteria and fungi, and forming the largest source of all, the activities of marine organisms. Natural mechanisms have been able to handle the complex interactions between all these naturally produced compounds under a wide range of climatic

conditions. The present world-wide pollution problems have developed only since the advent of uncontrolled burning of fossil fuels and the development of the chemical manufacturing.

ADVERSE HEALTH EFFECTS

INTRODUCTION

In 1985, the American Thoracic Society (ATS) published 'Guidelines as to what constitutes an adverse respiratory health effect, with special reference to epidemiologic studies of air pollution'. Perceptions of 'medical significance' and 'normal activity' differ markedly even between physicians, and depend greatly on individual circumstances. As a result, it was considered at that time to be virtually impossible to develop objective and generally applicable definitions. The ATS Advisory Committee therefore decided to recommend that 'adverse respiratory health effects' should meet one or more of the following criteria:

- the interference with the normal activity of the affected person or persons;
- episodic respiratory illness;
- incapacitating illness;
- permanent respiratory injury; and/or
- progressive respiratory dysfunction.

There remains, however, a range of interpretations of what is 'adverse'. The US EPA at the time had decided that a blood carboxyhaemoglobin level of greater that 2.5 per cent indicated a medically significant adverse affect, whilst irritation of the eyes, nose and throat during exposure to urban smog did not, despite the undoubtedly troublesome nature of the personal irritation.

The ATS Advisory Committee detailed a list of adverse health effects such as mortality, cancer and asthma; and largely non-adverse effects such as odour and upper airway irritation; but it admitted the wide ranges for interpretation. Various criteria are suggested for 'significance' in studies of health effects, and the situation was summarised by Samet (1985), in an editorial which accompanied the ATS statement. In a later review, Utell and Samet (1988) reassessed the relationships between health and air pollution, including indoor pollution, risk assessment and future research developments.

More recently, Bates (1992) presented his concept of "Coherence". In reviewing a number of papers which looked at different aspects of adverse health effects, he was impressed by the need to assess the necessary, or possible, interrelationships between the various different indices. Bates proposed that a basic differentiation was to assess whether the various indices

related to discrete episodes of air pollution, or whether they were more related to long-term effects.

He noted that the interrelationship between the two types of observations was often obscure and rarely discussed.

Episodic Data:

These include, during episodes of increased pollution:
- increased respiratory mortality
- increased hospital respiratory admissions
- increased hospital respiratory emergency room visits
- increased physician visits or ambulance use
- decreases in FEV_1 or PEFR
- symptom variation
- changes in various indices of ill-health such as school or work absences or "reduced activity days".

Long-Term Data:

In addition to the above observations, there is a series of non-episodic or long-term data:
- increased mortality from respiratory disease in regions of higher pollution
- changing mortality from respiratory disease in the same region as pollutant levels change
- increased prevalence of symptoms or of respiratory disease indicators in regions of higher pollution
- cross-sectional FEV_1 differences between regions with different pollution.

Bates went on to propose as the basis of his 'Theory' of Coherence, that it is useful to categorise associated findings as *'contingent'* (meaning that if the principal finding is true, then the 'contingent' finding has to be present), *'probable'*, and *'possible'*. Although this classification is based on individual judgement, the absence of a 'contingent' finding should throw doubt on the significance of any original observations, whereas the 'probable' or 'possible' categories might be considered "optional". Thus in any examination of possible/probable pollution related adverse health effects, one should be able to first classify, and then determine the degrees of coherence for any set of relationships and thereby assess the strength or otherwise of cause and effect.

ASTHMA AND RELATED CONDITIONS

At least 40 per cent of the population have what might be termed an allergic tendency; but whilst an individual may 'naturally' have an underlying tendency to exhibit greater sensitivity, a number of external factors are important in determining his/her eventual response pattern.

Asthma is characterised by the presence of increased irritability of the air passages which results in episodic spasm of the muscular walls of the smaller air passages, associated with increased mucous production and irritability of nerve endings leading to persistent coughing. With time, if the irritation remains uncontrolled, the asthmatic episodes can become progressively more severe, and can culminate in crises which can be fatal. On the other hand, many individuals have marked degrees of air passage sensitivity which is normally latent, but which can be actively provoked, often dramatically, by relatively minor stresses such as viral infections, or exposure to allergens, recognised irritants (such as tobacco smoke), or to less obvious irritants such as air pollutants such as sulfur dioxide, ozone, nitrogen dioxide, or respirable particles.

There is now a good body of objective experimental and clinical evidence to indicate that reproducible changes occur not only in the epithelial lining layer of the airway walls, but also deeper within the muscle walls of airway. As a result, secondary changes occur in the muscle layers, in the mucous glands of the airway walls, in the populations of cells which inhabit the epithelial layers, and in the lumens (spaces) of the airways. These changes bring about a persistent (chronic) contraction of the muscle layers, causing narrowing of the airways. The end result is a measurable decrease in the effectiveness of the normal mechanisms which protect the lung, leaving the way open for more frequent and more serious respiratory infections.

In the longer term, increased irritation and infection can produce various structural changes in the airways which are generally irreversible. Although for many individuals the changes may seem to be relatively minor and inconsequential, where whole communities are involved the long-term costs for health care escalate rapidly.

Over the past two or three decades there has been an apparent increase observed in both the incidence and the severity of asthma in places as far apart as Australia and New Zealand, the United States and parts of Western Europe; and there has been an overall increase in the death rate from asthma. The deteriorating environmental conditions in many western countries have been implicated in many of the hypotheses put forward to explain these trends; but at present they remain hypotheses only, no firm conclusions having yet been reached. Indeed, it is reasonable to conclude at this time that there is as yet no good evidence to suggest that exposure to air pollution actually causes asthma, although there can be no doubt that air pollution can aggravate and exacerbate pre-existing asthma (or bronchial hyper-reactivity). The Six Cities Study has shown that although there was no association between wheeze in children and pollution level, children with wheeze had a higher prevalence of cough and bronchitis than non-wheezy children, and a steeper gradient of symptoms across increasing levels of pollution.

Despite the lack of definite evidence of a relationship between air pollution and asthma (or bronchial hyper-reactivity), there is good evidence from a number of studies which have looked at individuals of all ages that following constant exposure to known respiratory tract irritants, often in relatively low concentrations, airways tend to react more readily and to develop an 'asthmatic' type of response (an 'asthmatic' response can be defined as showing evidence of increased airway reactivity on non-specific provocation testing.) Once this 'asthmatic' response pattern has developed, it appears to persist for an extended period, although it may well lessen slowly with time if the individual is removed entirely from the irritant atmosphere. In many instances however, the changes are irreversible. This pattern of response has been observed in infants and young children who have been constantly exposed to tobacco smoke, especially by the mother; and in adults exposed to known occupational irritants.

CHRONIC BRONCHITIS

Chronic bronchitis is a clinical state in which there is persistent coughing and mucus (sputum) production for at least three months of the year (usually during the winter), and for more than two consecutive years. It is characterised by marked enlargement of mucus glands in the walls of the air passages, irritable airway muscles, excess mucus production, and a general thickening of the air passages themselves. Once established, it is generally irreversible; and in the Australian community it is generally a result of tobacco smoking. The structural changes seen in the air passages with chronic bronchitis are those which one would expect to see in any tissue which is chronically exposed to irritants, be they inert particles of tobacco ash, coal ash, soot, carbon particles, iron particles, silica or the like; or reactive chemical compounds such as combustion products found in tobacco smoke or in many industrial situations.

Chronic bronchitis has been associated with air pollution for many years in the Northern Hemisphere, with its high sulfur dioxide and particle contamination. Epidemiological studies in both Europe and North America have repeatedly demonstrated the relationship between the two. In Australia, with no significant generalised sulfur dioxide air pollution, there is little evidence to relate air pollution and chronic bronchitis, especially in younger people, without the added aggravation of tobacco smoke, although subjective evidence suggests that pre-existing chronic bronchitis and related chronic bronchial inflammatory conditions may be aggravated by exposure to peaks of photochemical pollutants (ozone and nitrogen dioxide), and peaks of air-borne particles. When these peaks are also associated with colder weather and viral infections, chronic bronchitis can be considerably exacerbated, and pneumonia may result.

In Australia, tobacco smoke is the major cause of chronic bronchitis, and the major factor aggravating existing chronic bronchitis, both winter and summer. In some parts of the country, wood smoke from domestic fires causes considerable particle pollution in association with local geographic factors and wintertime inversion layers. These 'events' can be prolonged over several days, they are often associated with significant peaks of nitrogen dioxide, and invariably lead to significant increases in community morbidity for acute infective exacerbations of chronic airways disease in both the young and the old. Around 95 per cent of chronic bronchitis in this country can be attributed to tobacco smoke, while all other industrial and environmental factors together account for only 5 per cent.

MORTALITY

In past decades, there have been a number of major pollution episodes which have resulted in significant increases in daily death (mortality) rates. An often quoted example is the 'smog' episode in London in late 1952 when, over about one week, there were approximately 6000 extra deaths as a result of high concentrations of soot particles, fog, and sulfur dioxide, resulting in a sulfuric acid mist. These episodes attracted very considerable community interest, and often lead to governments enacting legislation to prevent recurrences. The statistical analyses used to study the effects of these pollution episodes on the communities in question were however fairly crude and insensitive, usually some form of cross-sectional analysis, so that they lacked sufficient power to look at the effects of much lower ('normal') levels of pollution.

With the advent of newer, more sophisticated statistical techniques, in particular ' time-series' analysis, it has become possible to show the weaknesses of the earlier statistical methods, and to now demonstrate, with increasing strength or power, robust relationships between community illness patterns (morbidity) and death (mortality) rates and air pollution in concentrations which, less than a decade ago, would have been usually regarded as being well within 'acceptable' harmless limits unlikely to cause injury to anyone but possibly the most sensitive and susceptible members of the community.

Since about 1990, numerous studies have been undertaken and published examining the relationships between air pollution, both as a mixture of compounds, and also the various compounds individually against each other, whilst allowing for external factors such as seasonal variation, temperature, time delays and the like. Although most attention has been focussed on particles of various sizes and characteristics (total suspended particulates (TSP) or respirable particles (PM_{10}), and in the last few years, finer particle fractions such as $PM_{2.5}$, and the 'ultrafines'), increasingly studies are looking at the measurable effects of pollutant gases such as ozone, nitrogen dioxide, and sulfur dioxide.

It is now apparent from studies undertaken around the world, that there is a relatively constant association between particle pollution and mortality of the order of a 1% increase in daily mortality patterns for every 10 μg/m³ increase in respirable particle concentrations, but without any obvious 'threshold' level yet being apparent. This relationship has been shown to apply in cities on most continents, as widely separated as Philadelphia - Santiago - Sydney - London - Athens - Mexico City - Los Angeles - Toronto - and so the list grows.

The mechanism for this mortality effect has not yet been defined although there are a number of hypotheses have been put forward. These are discussed in some detail later in this review, but what does appear to be certain is that healthy individuals are not affected by the adverse effects of particles as such, rather the adverse effects are seen in those who are already compromised with acute or chronic heart and/or lung disease, the elderly and the very young. Likewise the mechanisms leading to the mortality effects resulting from exposure to ozone, nitrogen dioxide, etc., have yet to be defined. Increased hospital admissions and deaths from cardiac causes are rather more features in this context.

Mortality effects are much more strongly related to daily exposures, often with a 1 - 2 day lag after exposure, than they would appear to be when long-term (such as annual) exposures are assessed. This is not to say that other health effects such as cough, sputum production, wheeze, increased frequency of chest infection, chronic bronchitis and related conditions can not be demonstrated - far from it ! Rather the statistical relationships between longer term exposures and mortality are weak at this time, and it will be necessary to wait on the development of even more powerful and sensitive statistical tools before any conclusions can be reached.

CANCER, VOLATILE ORGANIC COMPOUNDS AND AIR TOXINS

Over the past decade, a considerable body of experimental evidence has been accumulated on the potential for tumour induction in a community following the release of a range of toxic materials, generally hydrocarbon in nature, from both stationary and mobile sources.

The USEPA in 1983 commissioned a review of current evidence for an association between cancer and air pollution (USEPA 1983). Again tobacco smoking far outweighed other factors. The situation is complex, and may be further complicated by factors such as genetic background, diet, alcohol, sunlight or industrial exposures, all of which may be involved in the aetiology (causation) of a tumour. In addition, the majority of human tumours have a long latency period, generally a minimum of 12-15 years and often much longer, so that aetiologically significant air pollution exposures may be forgotten or masked. In Australia, along with other immigrant 'receptor' countries such as Canada, South Africa, New Zealand and the United States, there is a general increase in cancer incidence, quite apart from the effects of

tobacco smoke and possibly alcohol, among people who have emigrated either before or since World War II from heavily industrialised countries in north-western Europe. This increase is not seen among their descendants born in the 'receptor' countries, and so not exposed in childhood, adolescence or young adulthood to the environmental contaminants of north-western Europe.

Tobacco smoking has been conclusively implicated in a very significant increase in cancers of the respiratory tract, and to a lesser degree, of some other systems, including the gastro-intestinal system and the urinary system (bladder, prostate, kidney). Tobacco smoke contains about 4,000 different chemicals including a number of known carcinogens, several of which are discussed in this review - arsenic, radionuclides, cadmium, vinyl chloride, acrylonitrile, benz(α)pyrene and other polycyclic aromatic hydrocarbons; a range of other combustion products including formaldehyde, hydrogen cyanide, and carbon monoxide; insecticide residues (including DDT); ammonia; solvents such as benzene, acetone and toluene; dibenzacridine, and nitrosamines.

This same range of compounds is found in the emissions of any combustion source burning organic materials, including domestic incinerators, slow combustion stoves, wood fires, agricultural and forest burning, and automobile exhausts, especially diesel exhausts. Further studies in the United States have identified areas of concern, which are explored in detail in a review chaired by Gordis and Kuller (1986).

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SUMMARIES OF HEALTH EFFECTS

CARBON MONOXIDE

Several major reviews of the health effects of carbon monoxide (CO) have been published in recent years (Concawe 1997, Bascom et al 1996, WHO 1996, DoE 1996, DoE 1994, Health Canada 1995, USEPA 1992, USEPA 1991, Streeton 1990, WHO 1987, Environment Canada 1987, USEPA 1979, WHO 1979). In addition, both WHO 1979 and WHO 1987 recently have been revised but not yet published (Maynard 1996, 1997). There have been no significant variations in the approaches adopted by the various national and international jurisdictions to the adverse health effects of CO over this time, namely that to achieve adequate protection of the more susceptible population sub-groups (those with ischaemic heart disease; those with other forms of cardiac disease including cyanotic heart disease; hypoxaemic lung disease; cerebrovascular disease; peripheral vascular disease; those with anaemias and haemoglobin abnormalities; children; and the developing foetus), a carboxyhaemoglobin level of not more than 2.5% whilst either at rest or during active physical exercise should not be exceeded.

The linear relationship that exists between CO and haemoglobin ensures that predictable levels of COHb will be achieved for a given ambient concentration, for a given duration of exposure, and at a given level of rest or exercise. CO has the added 'advantage' in that unlike the other gaseous ambient pollutants, it has no interaction with lung tissues or structures but rather it diffuses directly across the alveolar membrane to combine with red cell haemoglobin within the pulmonary capillary network. As haemoglobin has some 220 times more affinity for CO than it does for oxygen, rapid transfer across the membrane and uptake by the red blood cells is assured, this uptake being enhanced by the increase that occurs in ventilation during exercise.

Over the past two decades, research has focussed on the characterisation of cardiac health effects in persons with ischaemic heart disease, a group regarded as the most sensitive to the adverse effects of CO. Protection of this group has been the basis for the air quality standards that have been applied in jurisdictions around the world. The impact of even minor increases in COHb levels have been consistently demonstrated in both controlled exposure studies and in community epidemiological reviews, with the clear message that a reduction in community levels of exposure to CO should reduce the occurrence of ischaemic episodes and the consequent increase in risk for acute myocardial infarction. There is no valid evidence to support claims that CO exposure leads to the development of atherosclerosis, but rather that the atherosclerotic process results from, or is aggravated by, some components of tobacco smoke.

Healthy persons are unlikely to be significantly affected by ambient levels of CO with regard to possible limitation of exercise capacity, and neuro-behavioural effects are unlikely at COHb levels of less than 15 - 20%.

Maternal smoking is well recognised as a significant cause of reduced birth weight and delays in foetal and neonatal development, and would appear to be reasonably attributed to CO exposure at levels of COHb between 2.0% - 7.0%.

Protective Concentration Ranges

As indicated above, there has been universal agreement around the world that for adequate protection of susceptible populations, CO concentrations in ambient air (indoors or outdoors) should be such that no matter what duration of exposure or level of exercise activity, COHb concentrations should not exceed a recommended No Observed Effect Level (NOEL) of 2.5%.

In most jurisdictions, there has been a trend to establish air quality standards / guidelines / recommendations based not only on exposure periods by which equilibration will be achieved (8 hours or more), but also based on shorter periods to control for the potentially adverse effects of more intense but shorter-lived exposures. By use of the Coburn-Forster-Kane (CFK) equation, allowance can be made for the recognised physiological variables known to effect CO uptake by an individual, either healthy or compromised. In this way, periods of time-weighted average exposures and CO levels can be determined in order to ensure that the COHb level of 2.5% is not exceeded in any exposed individual, even when that individual is engaged in heavy manual work.

In developing suggested ranges for protective concentrations, not only is it necessary to provide protection for susceptible populations, especially those with ischaemic heart disease, it is also desirable to ensure that an appropriate safety factor is incorporated to protect the most sensitive groups of all, namely those identified as suffering from clinical angina. Using the CFK equation, it can be shown that in an individual at rest, the CO concentration producing a COHb level of 2.5% after 8 hours exposure is 15 ppm. It is usual public health practice to apply a safety factor of 1.5 times the NOEL , thus reducing the safe ambient CO concentration to 10 ppm.

At a concentration of 10 ppm, a continuously exposed non-smoking population would have COHb levels which should not exceed 1.6%. This relationship applies whether the individual is sedentary, or undergoing heavy physical activity. By basing the primary exposure standard / guideline on an 8-hour averaging time, there should be sufficient protection for the population as a whole against continuous lifetime exposures. By extrapolation, CO concentrations relating to shorter averaging periods can also be estimated, including a safety factor, even although at these shorter exposures, equilibrium through the various body compartments will not have

been achieved. These shorter averaging period guidelines are especially important in situations where there is potential for more intense exposure, such as in dense slow-moving traffic in street canyons, in tunnels, in underground or enclosed carparks, etc.

A review of recommended standards / goals / guidelines from around the world indicates universal acceptance of an eight (8) hour exposure standard of 9 - 10 ppm, with shorter term one (1) hour exposure standards ranging between 25 - 30 ppm (the differences mainly relate to the use of differing correction factors for temperature at atmospheric pressure). Current standards / guidelines here in Australia (NHMRC and State) all conform closely to international standards / guidelines.

More recently, WHO (1995) has indicated in draft guidelines yet to be published that additional shorter term guidelines to protect for more intense, but short-lived exposures, such as might occur in enclosed situations such as tunnels, etc., should be considered.

 These shorter term guidelines include:

(a) 90 ppm for a 15 minute average exposure period, and

(b) 50 ppm for a 30 minute average exposure period.

In the Australian context, it is our impression that the 1-hour and 8-hour standards are rarely, if ever, exceeded in Australian cities, with the one exception of Sydney where a number of exceedances have been recorded each year for the past several years.

LEAD

The earliest recognised effect of lead exposure is a decrease in intelligence and general academic performance in children resulting from exposure within the first 2-3 years of life. There is now clear epidemiological evidence of a close causal relationship between prenatal exposure to lead (as measured by umbilical cord blood) and early mental development indices.

This effect has been attributed to lead present at blood levels as low as 10 μg/dL, but the absence of any identifiable threshold level suggests that a deleterious effect may be produced by blood lead levels lower than 10 μg/dL (< 0.48μmol/L). Lead may exert its effects by substituting for calcium in critical biochemical reactions.

Recent studies have raised the possibility that low levels of lead may increase blood pressure in adults. This may increase the risk of stroke and coronary artery disease over a population with consequent increases in both morbidity and mortality. The statistical significance of these observations is however low at this time (not more than 5%).

Regulatory agencies in the United States, Canada, Australia and elsewhere have developed policies to reduce blood levels of lead to 10 μg/dL (not greater than 0.48 μmol/L) or less for all of their populations, from the youngest to the oldest although clearly some groups are at more potential risk for adverse effects from lead than are others. Table 3 (Appendix 2) later in this review sets out in summary the various adverse health effects that have, thus far, been identified as causally related to lead.

In countries where lead is used as a petroleum additive, the majority of airborne lead in urban areas (at least 75%, and probably greater in some situations) is derived from this source. Airborne lead levels of up to 10 μg/m³ have been measured near areas of high traffic density. After the removal of leaded petrol, airborne levels in urban areas commonly fall to below 0.2 μg/m³.

At present the major routes for lead intake for both children and for adults are by inhalation and by ingestion. Lead particles emitted from vehicle exhausts fall into the 'fine' (less than 2.5 μm) and 'ultra-fine' (less than 1.0 μm) fractions, and as such, are readily inhaled and deposited in the respiratory tract. Ingestion of dust or soil containing deposited lead particles also makes a major contribution to the intake of lead in young children who live near major roads or near point sources (smelters, etc) of lead exposure where extensive deposition of lead in soil has occurred. Unlike other exposure sources which are declining, contaminated soil and dust are likely to remain as important exposure sources well into the future.

Airborne lead is a potentially important exposure source because of the relatively high levels of systemic absorption from the lungs. There is good evidence to suggest that of the order of 75% of inhaled fine particulate lead is absorbed from the airways, and is thus available for metabolism. However, absolute air levels are falling sharply in areas where restrictions on leaded petrol have been introduced. Apart from those individuals living near point sources of exposure, airborne lead levels can be expected to contribute decreasingly to the overall lead burden as the proportion of leaded petrol consumption falls in relation to total fuel sales.

The present air standard for lead exposure (1.5 $\mu g/m^3$ as a rolling quarterly mean) was established at a time when the detailed knowledge of the adverse effects of lead on the developing nervous system was less advanced. Continuous inhalation of air containing this level of lead would be expected to raise blood lead levels by between 1.5 - 3.0 $\mu g/dL$. Considering the present philosophy of attempting to maintain blood lead levels as low as possible, a strong case can be made for revising this standard downwards, perhaps to 0.3 $\mu g/m^3$. The indicator of outcomes would be by high volume air sampling, and in some circumstances lead levels in dust. For individual exposures, direct blood lead estimation remains the most appropriate method.

In conclusion, it is suggested that in order to establish an optimum ambient concentration for airborne lead so that appropriate protection from the adverse health of lead can be achieved for the whole population, ambient lead levels should be held in the range of 0.3 - 0.5 $\mu g/m^3$ on a mean moving monthly (or as an annual) standard, but NOT to exceed 0.5 $\mu g/m^3$ at any time. Therefore a national standard or guideline of 0.5 $\mu g/m^3$ as a moving monthly mean, not to be exceeded, and reviewed not more than every five (5) years would appear to be the proper approach in 1997. Ambient levels of this order should adequately protect the range of risk groups in the community, from unborn foetuses, infants, and young children through to the general adult population.

NITROGEN DIOXIDE

An assessment of the adverse health effects of nitrogen dioxide (NO_2) presents a somewhat conflicting pattern of disturbances in respiratory function, increase in lower respiratory tract symptoms in children, aggravation of asthma, impairment of lung defences, and more recently, a suggestion of an effect on daily mortality, particularly in older compromised adults. It is quite probable however that the conflicting epidemiological data reflects the known interactions between NO_2 and other pollutants, in particular, fine respirable particles ($PM_{2.5}$) and ozone (with which NO_2 bears an inverse relationship).

Statistical reviews of the available epidemiological and controlled exposure data, based on predominantly short term ambient exposures, would suggest that the current lowest observed adverse effect level (LOAEL) is in the range of 0.2 - 0.3 ppm, however there is an increasing body of data to suggest that longer term chronic indoor exposure to significantly lower concentrations of NO_2, of the order of 0.04 - 0.08 ppm during early and middle childhood years can lead to the development of recurrent upper and lower respiratory tract symptoms, such as recurrent 'colds', a productive cough and an increased incidence of respiratory infection with resultant absenteeism from school.

A safety factor needs to applied to any LOEL in order to ensure adequate protection of the more vulnerable sub-groups in the population - the young, asthmatics of all ages but especially children, and compromised adults with chronic respiratory and cardiac disorders. Currently, this safety factor is generally regarded as being of the order of 50% of the LOEL, which would suggest that standards / guidelines should be in the range: 0.10 - 0.15 ppm for shorter term exposures (1 hour averaging period), and in the range: 0.02 - 0.04 ppm for longer term exposures (annual averaging period) to ensure there is adequate protection for the more susceptible individuals in the community.

PHOTOCHEMICAL OXIDANT (AS OZONE)

Ozone is a highly irritant substance which has significant effects at various levels of the respiratory tract from the nasal passages to the alveolar epithelial membrane, now well described by many authorities.

There is strong supportive evidence of clinical, epidemiological and controlled exposure associations with ozone at ambient levels normally encountered in Australian cities. These exposures result in a range of acute health effects which include minor changes in lung function, increasing symptoms consistent with upper and lower airway irritation, leading to an increased requirement for additional medication, increased requirement for medical services such as attendance at medical surgeries, hospital casualty departments, and hospitalisation.

There is also evidence of a slight but definite increase in mortality, chiefly from cardiovascular causes, particularly in the elderly, following ozone exposure.

Population studies recently undertaken in Sydney which assessed various health outcomes including morbidity and mortality confirmed previous assumptions that the literature on the adverse health effects of ozone observed in North America and Europe is reproducible in Australia, and there is no reason why similar response patterns would not be observed in other larger Australian cities.

There is consistent evidence to suggest that there are specific subgroups within the population which are more susceptible to the adverse health effects of ozone, in particular, asthmatics. In addition, there is an increasing body of literature which details the various interactions between the pollutants ozone, nitrogen dioxide, particles, and to a lesser extent in the Australian context, sulfur dioxide. In particular, there is robust statistical data which supports enhancement of the effects of ozone, as a result of prior or concurrent exposure to particles, nitrogen dioxide, airborne allergens, and to sulfur dioxide, collected in a wide range of environments in many countries. Meteorological factors such as temperature have also shown influence. The coherence of the relationships of pollutants and the many associations of effects, including mortality events leaves little doubt as to the validity and the strength of assumptions of causality.

Animal toxicological evidence is supportive of the human clinical observations which suggest that the primary mechanism of action of ozone is the induction of vigorous inflammatory responses, which in turn lead on to acute adverse respiratory events. Certainly in the context of short-term exposures, it is proper to conclude that the associations are causal.

In the context of longer term or chronic exposures, the epidemiological and experimental evidence is much less certain. In experimental animals, it is possible to demonstrate the development of an inflammatory bronchiolitis at the level of the respiratory bronchioles, however in human subjects, there are only suggestions of adverse response patterns and then usually only in the context of high levels of chronic exposure with worsening asthma, increased rates of functional decline in adults, impairment of normal lung growth in children, and possible changes in pulmonary immunological function especially in children. Considerable experimental work remains to be undertaken in this regard.

Previously, it has routine practice to express ozone goals or guidelines in terms of short exposures, generally of 1 hour; and in terms of a longer period of exposure, generally 8 hours. This approach ignores however the natural time frame for the evolution of the cycle of photochemical reactions in the atmosphere which normally take some 4 to 6 hours to develop during daylight hours. On the other hand, the evolution of the human inflammatory response patterns occurs over a much shorter period, usually only a few hours (1 - 3hours), and a strong argument can be made for having the primary goal or guideline maintained at a shorter interval to allow suitable control of the acute clinical responses, particularly in the more susceptible groups such as asthmatics, or exercising but otherwise healthy young adults.

No threshold exposure levels can be identified for ozone.

There is a monotonic relationship between increasing ozone concentration and adverse health effects. It is therefore not possible at this time to define either a No Observed Effect Level (NOEL), or a Lowest Observed Adverse Effect Level (LOAEL) for ozone.

Suggestions for suitable protective goals, standards or guidelines must therefore be based on directly observed measurements, whilst keeping in mind that natural factors including local vegetation and the proximity of the sea are significant sources of ozone, quite apart from ozone derived from anthropogenic sources. These observations are emphasised when it can be demonstrated that outdoor workers, such as those described recently from British Columbia, can be shown to lose significant functional capacity over the summer working period at ozone levels which are barely above background levels. A short-term goal or guideline clearly would not be protective in this context.

Therefore it is suggested that the averaging period for the primary goal or guideline for ozone should be (6 -) 8 hours on a rolling basis over daylight hours, with ozone levels for that period averaging between 0.05 - 0.06 ppm (50 - 60 ppb),not to be exceeded. A goal or guideline of this order should give adequate protection for those healthy individuals required to exercise outdoors over longer intervals of several hours, or indeed for the full working day.

A shorter term goal or guideline should be considered to achieve adequate protection for the clinically compromised in the community as a asthmatics and also young children who may be also exposed to other irritants such as indoor nitrogen dioxide. The margin however between clinical effect and background is very narrow. It is suggested therefore that a short-term 1 hour goal or guideline should be only marginally greater than the longer term primary goal or guideline, and ozone levels in the range 0.08 - 0.09 ppm (80 - 90 ppb), not to be exceeded, are suggested for consideration in order to achieve protection of the more susceptible individuals in the community.

RESPIRABLE PARTICLES

Over the past decade, evidence that human exposure to inhaled respirable particles can result in significant increases in both morbidity and mortality has become overwhelming. The following literature review details the development of scientific awareness and understanding of adverse health impacts which have thus far been identified and replicated around the world. Widely dispersed populations around the world have been assessed and have shown similar response patterns in every instance where appropriate statistical analyses have been undertaken.

It is now possible to enumerate the adverse health effects that have, on epidemiological, clinical and toxicological grounds been currently identified as being causally related to short-term increases in ambient respirable particles (PM_{10}). These associated adverse health effects include:

- increases in total mortality ('all causes'), as well as in mortality from respiratory or cardiac disease, of the order of 1% for every 10 μg/m3 increase in PM_{10} levels.

- increases in hospital admissions for respiratory, and (probably) cardiac conditions,

- increases in hospital casualty and medical surgery visits for asthma and other respiratory conditions,

- increases in functional limitation as indicated by restricted activity days or, in the case of children, by increased frequency of absence from school,

- increases in the daily prevalence of respiratory symptoms, and

- small decreases in the level of pulmonary function in healthy children, and in adults with obstructive airways disease.

These observations are consistent across many studies and provide a cohesive picture in that there are effects on many different respiratory health outcomes, however there remain legitimate questions as to the causal nature of these associations. Many questions remain, and centre on major issues such as the plausibility of the possible/probable associations, details of exposure, proper disease classification and the use of inappropriate and/or inadequate statistical analytical methods.

There are population subgroups that are clearly more sensitive to PM_{10} exposure, in that they experience more severely adverse health effects for a given particle exposure. These subgroups include the elderly (as a whole) and those individuals suffering from pre-existing heart or lung disease. There is also evidence to suggest that young children may be more sensitive, leading

to an increased frequency of respiratory tract infections, coughing, and wheezing.

There is satisfactory evidence at this time that PM_{10} pollution produced from natural or crustal sources is significantly less harmful than PM_{10} generated from combustion processes, although in situations of extreme exposure such as with volcanic eruptions, significant long term respiratory damage can result.

Statistical evidence at this time suggests that the observed adverse health effects of PM_{10} appear to occur independently of the presence of other pollutants such as ozone, nitrogen dioxide, and probably sulfur dioxide, although the reverse does not apply. There is evidence to suggest that PM_{10} can impact significantly as a major confounder on the observed responses to other pollutants such as those listed above, however there is no satisfactory evidence that the effects of PM_{10} are potentiated by other pollutants.

At the present time, there is no evidence, based on epidemiologic data, that threshold concentrations can be described for PM_{10} below which it is not possible to detect any population impacts. With progressive refinement of statistical method leading to increasing sensitivity of detection, the lowest observed effect levels have been steadily reducing in recent years.

There is no available evidence to give credence to the hypothesis that, for equal daily concentrations, high particle concentrations for brief periods are more harmful than relatively constant low level concentrations. Further research is required before any useful progress can be made towards establishing air quality goals or guidelines based on short-term exposures. At the present time, there it would seem that goals or guidelines based on 24-hour average measurements should be sufficient to adequately protect population health. An alternative option could be to base air quality goals or guidelines on increases in PM_{10} concentrations rather than on absolute PM_{10} concentrations. Focussing on the frequency of daily 10 $\mu g/m^3$ PM_{10} increments above an absolute concentration of 10 $\mu g/m^3$ is a starting point given the weight of current scientific evidence. This is the approach currently being considered by the WHO Working Group (Dr. R. Maynard, personal communication), and determination of the numbers of PM_{10} increments that might be considered acceptable has to be based on the acceptability (to the particular population in question) of the various health impacts health impacts predicted for the selected numbers of PM_{10} increments.

Currently, the evidence that particles of some particle size ranges ($PM_{2.5}$, $PM_{1.0}$) seen within the PM_{10} fraction might be more deleterious to health than others size fractions is of varying strength, although there is increasing evidence to suggest that the $PM_{2.5}$ fraction (fine particles) may well be the major area of concern with regard to adverse health effects. With these emerging trends in mind, there would appear to be

compelling reasons for basing ambient particle goals or guidelines on the fine particle fraction, rather than concentrating on the larger Inhalable particle fraction (coarse particles or PM_{10}). More recently, concerns are being raised as to the weighting that may or not be required to be put on smaller particle fractions such $PM_{1.0}$, or even smaller (ultrafine particles). At this stage of things, there is no supporting data to suggest that this fraction is necessarily of major concern in the long-term, certainly when compared to the clearly increasing role of the $PM_{2.5}$ fraction. Decisions regarding the size range of particles to be monitored will have major implications for the monitoring networks already in place.

There is no convincing evidence yet to hand which suggests that chronic health problems are being caused by long-term exposure to PM_{10} pollution, independent of the effects due to repeated short-term exposures. Longer term health effects may well be related to chronic exposure to other pollutants, such as NO_2, SO_2, and possibly O_3. There is at this time no compelling evidence to support a health based annual average air quality goal or guideline, although such a value may be of assistance in achieving longer term aesthetic goals. The main thrust for controls, based on health effects, must be towards a short-term objective. Indeed, there is good evidence to suggest that currently observed health effects are occurring at particle levels well below current annual standards.

World Health Organisation - European Region (WHO-EURO) has prepared revised Air Quality Guidelines for a various air pollutants, including particles. The earlier guidelines(1987) were based on the premise that there were no observable adverse effects levels (NOAELS)and that public health could be protected by establishing a lower concentration limit than the NOAEL using a safety factor. The latest WHO-EURO expert committee for particles concluded that there was no current basis for establishing a NOAEL for particles. It has recommended instead that exposure-response relationships for PM_{10} and $PM_{2.5}$. as interpreted and tabulated by the expert panel, be reported with tabular guidance and interpretive text for use by national authorities in establishing their own air quality standards. Thus, the burden of decision is to be put back on to the various national authorities to determine their own acceptance limits for the public health impacts of exposures to ambient respirable particles.

Another recent report from the U.K. (DoH 1995) concluded that "In terms of protecting public health it would be <u>imprudent</u> not to regard the demonstrated associations between daily concentrations of particles and acute effects on health as casual".

Finally, the most thorough and comprehensive report now available is the new US EPA Particle Criteria Document (US EPA 1996a).

Among its numerous conclusions are:

- The chemical and physical differences between fine-mode and coarse-mode particles have important implications for evaluation of the health and welfare effects of such particles as distinct pollutant subclasses.

- Our current understanding of the toxicology of ambient particulate matter suggests that fine and coarse particles may have different biological effects.

- The evidence of PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, mis-specification or concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure other than PM, weather, or other variables, nor confounding of PM effects with effects of other factors.

- Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles, thoracic particles (PM_{10} or PM_{15}), and sulfate ($SO_4^=$). Less consistent relationships have been observed for TSP, strong acidity (H^+), and coarse PM (PM_{10} - $PM_{2.5}$).

- There is evidence that older adults with disease are more likely to be impacted by PM-related health effecters (including mortality) than are healthy young adults. The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by :

  1. the more uniform distribution of fine particles across urban areas and their well-correlated variation from site to site within a given city;

  2. the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time);

  3. the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

Other points include:

- Based on theoretical, experimental and observational scientific evidence, the pathogenic effects attributable to particles in the inhalable fraction are largely, and possibly exclusively, due to the effects of particles in the fine fraction.

- Based on the concentration-response relationships observed by $PM_{2.5}$ and for PM_{10} it is reasonable to maintain that adverse health effects related to increases in fine particle concentrations begin to occur at a concentration of approximately 20 ug/m3.

- A reasonable recommendation, if feasible, would be to base air quality objectives or standards on fine particle concentrations while maintaining the capability of monitoring concentrations of inhalable particles, with or without continuing to maintain objectives or standards based on inhalable particle concentrations as well.

- There is no strong evidence available at this time that fine particle objectives or standards should be base don averaging times shorter than 24 hours.

- Although there is historical precedent for objectives and standards based on annual average particle concentrations, there is no evidence that an annual average provides additional information of relevance to the adverse health effects of particles beyond that available from daily averages alone.

- Although there is some scientific support for fine particle chemical composition being important in determining pathogenic particle effects, the evidence that would support inclusion of some aspect of particle chemical composition in the fine particle objectives or standards, beyond that already accounted for by focusing on the fine fraction alone, is contradictory and therefore not compelling.

Suggested 'Protective' Ranges:

PM_{10}: 24 Hours: 50 μg/m^3

$PM_{2.5}$: 24 hours: 20 - 25 μg/m^3

NO 'ANNUAL' Range is proposed at this time.

Consideration could be given to the later introduction of a guideline/standard based on exposure - response relationships.

SULFUR DIOXIDE

Sulfur dioxide (SO_2) exposure results in the development of an acute irritant response initially in the upper airways (nose, throat, trachea and major bronchi) leading to coughing, wheezing, sputum production, increased incidence of respiratory infections, aggravation of asthma and chronic obstructive airways diseases, with resultant measurable increases in community patterns of respiratory and cardiovascular morbidity and mortality. The asthmatic population is at particular risk, and experimental studies have repeatedly demonstrated that SO_2 exposure in susceptible individuals can result in a rapid onset of symptoms and impairment of respiratory function within 10 - 15 minutes of exposure. Goals or guidelines need therefore to provide for adequate short-term protection for those susceptible individuals in the community, and it is suggested that an appropriate short-term goal or guideline should be in the vicinity of 0.175 ppm (500 $\mu g/m^3$). Longer-term goals or guidelines also need to be considered to protect both susceptible groups as well as the community as a whole in order to reduce overall the incidence of averse long-term effects of SO_2 exposure. It is therefore desirable to consider both daily (24 hour) and annual protective goals or guidelines, and it is suggested that appropriate values should be for a 24 hour protective goal or guideline 0.04 ppm (125 $\mu g/m^3$), and for an annual protective goal or guideline 0.02 ppm (50 $\mu g/m^3$).

Protective Ranges

Sulfur dioxide (SO_2) results, in the context of urban pollution, from the combustion of sulfur-containing fossil fuels such as coal and heavy oils. SO_2 has a direct irritant effect on the human airway, causing stimulation of protective nerve endings in the upper larger airways in the first instance. Individuals whose air passages are especially susceptible to irritant stimuli (asthmatics of all ages, those with chronic bronchitis and related conditions, and others who have compromised cardio-respiratory function) frequently respond by developing increasing coughing, chest tightness, wheezing, and aggravated sputum production. There is are considerable differences in the concentrations of SO_2 required to produce acute irritant responses in those individuals who have normal patterns of airway reactivity (1.0+ ppm), and in those individuals who have significantly increased airway reactivity such as asthmatics (0.2 -0.3 ppm).

At a community level, these individual irritant responses to SO_2 are manifest as an increasing frequency and severity of asthma, increased hospital admissions, aggravation of underlying respiratory infections, resulting in increases in both morbidity (illness) and mortality (death). In many instances, it is difficult, and at times impossible, to separate the adverse effects resulting from SO_2 exposure from those effects resulting from concurrent exposure to mixtures of other known irritant pollutants such as respirable particles, nitrogen   oxides,   and   ozone.   Prior

exposure to other pollutants is now recognised as resulting in a general accentuation of airway responses to other irritant stimuli, including allergens such as grass pollens, house dust, animal danders and the like. A useful review of the current understanding of the effects of mixtures of pollutants can be found in DoH 1995b (*"Health Effects of Exposures to Mixtures of Pollutants"*).

SO_2 acts directly on the larger upper airways (nose, throat, trachea, and major bronchi) in the first instance, responses tend to be generally rapid in onset, occurring within a few minutes, and achieving maximum effect within 10 - 15 minutes, particularly in those individuals with significant increases in airway (bronchial) reactivity, such as asthmatics and those suffering from other similar bronchospastic conditions.

These responses can be manifest either symptomatically as wheezing, chest tightness, shortness of breath or coughing; or functionally as reductions in ventilatory capacity ($FEV_{1.0}$, increased specific airway resistance[sRAW], or other like parameters of ventilatory function). If exposure to SO_2 should occur under exercise conditions, then the observed responses may well be accentuated due to increased ventilation associated with exercise, and the fact that soluble gases such as SO_2 will tend to carried much further down the respiratory tract before coming into contact with the lining mucus layer of the airways, the bronchial mucosa, resulting in the production of an irritant acidic solution which stimulates the sensory nerve endings (vagal afferents) leading to coughing and subsequently wheezing as a result of smooth muscle spasm.

There is a wide range of sensitivity present, both in normal individuals, and in those with asthma who recognised as being the most sensitive reactors to irritants such as SO_2. Whilst a threshold level has not yet been clearly defined, it is possible to demonstrate a pattern of continuous dose-response relationships. When considering protective ranges as part of guidelines or standards, it is clearly necessary to consider the minimum concentrations which can be identified with adverse effects, and for this purpose, it is usual to measure the responses occurring in asthmatics who are exercising in exposure chambers. It should be noted that the severity of the individuals asthma does not appear to greatly alter the pattern of response. In some studies, small changes were seen in airway resistance in a few asthmatic subjects at only 0.1 ppm (286 $\mu g/m^3$), however it is more usual to see minimal sub-clinical responses occurring at 0.2 ppm (572$\mu g/m^3$), a 10% reduction in $FEV_{1.0}$ below baseline at about 0.4 ppm (1144 $\mu g/m^3$), and reductions of about 15% in $FEV_{1.0}$ below baseline occurring at about 0.6 ppm (1716 $\mu g/m^3$). These results apply to short term exposures in an exposure chamber of approximately 15 minutes duration, both at rest and whilst under exercise conditions.

There do not appear to be any significant differences in observed responses to exposures of longer duration up to about 24 hours. Longer term (or chronic) exposures are more generally reflected in community patterns of respiratory illness, the prevalence of respiratory symptoms, or differences in lung function between areas of high or low levels of SO_2, usually with differing levels of particulates. Most of these studies were undertaken in coal-burning areas, and resulted in the LOAEL for SO_2, in combination with particulates, being considered to be 0.035 ppm (100 $\mu g/m^3$) annual average exposure. With changes in fuel burning patterns, and in urban mixtures, more recent studies usually related to specific industrial sources of SO_2 and changing urban situations would suggest LOAEL even less than 0.035 ppm. In the past , the influence of fine particles on morbidity and mortality patterns was not recognised as it is now, and indeed it would seem likely that the major effects are more probably related to the particle load than to other pollutants such as SO_2.

Medium term exposures of the order of 24 hour's duration have been assessed mainly using epidemiological studies in which the effects of SO_2, particulates, and other associated pollutants are considered. These studies mainly focus on the production of symptoms in groups of selected sensitive subjects, with symptoms generally developing when SO_2 levels exceeded 0.087 ppm (250 $\mu g/m3$), usually in the presence of particulates (PM10). More recent studies however take more regard of changing social activity patterns and changes in SO_2 sources such as mixed industrial and vehicular sources. These further studies are now showing increasing effects on mortality (all causes, respiratory, cardiovascular), and on morbidity (emergency hospital admissions for respiratory illnesses, especially COPD) at considerably lower levels of exposure than were previously thought to be the case, such as daily levels usually exceeding 0.043 ppm (125 $\mu g/m3$), or mean annual levels not exceeding 0.017 ppm (50 $\mu g/m3$). In some studies, these patterns of response have been shown to persist even when particulates expressed even crudely as black smoke or as TSP have been allowed for. It should be also noted that no obvious threshold levels have as yet been identified in these later studies.

To summarise the results of the available exposure data:

- Short-term protective exposure guidelines over brief periods of 10 - 15 minutes need to be considered as there is clear evidence in controlled studies that exercising asthmatics can be expected to experience some changes in lung (pulmonary) function in association with respiratory symptoms after short periods of exposure. As SO_2 can frequently present as brief sharp peaks, depending on the characteristics of the local sources, it is not practicable to extrapolate these short exposure periods into longer averaging periods such as 1 hour. Currently, the body of opinion favours the suggestion that any short term guideline should not exceed a concentration of 0.175 ppm (500 $\mu g/m3$) averaged over 10 minutes.

- Daily and longer-term exposures leading to changes in morbidity, mortality, or to alterations in lung function need to be assessed on the basis of available epidemiological studies where individuals are exposed to mixtures of pollutants, which usually, but not necessarily, include particulates. Previously, it was usual practice to base health related guidelines or standards on the observed LOAEL, corrected by a safety (uncertainty) factor of two to ensure adequate protection of susceptible individuals. However, as already indicated, more recent studies suggest the possibility of significant adverse public health effects at levels considerably lower than had been previously envisaged (for example, a 24-hour guideline of 0.04 ppm/ 125 $\mu g/m^3$; or an annual guideline of 0.02 ppm/50 $\mu g/m^3$). There remains considerable uncertainty as to whether or not SO_2 is in fact responsible for the observed adverse health effects, or whether it might be acting as a surrogate for an as yet unidentified pollutant, possibly ultra-fine particles. There as yet insufficient data available on which to base any further tightening of guidelines from those detailed above, as these previously suggested guidelines should provide adequate protection for the 'at-risk' asthmatic population in Australia.

APPENDIX 1 -
HEALTH EFFECTS OF CARBON MONOXIDE

SUMMARY

Several major reviews of the health effects of carbon monoxide (CO) have been published in recent years (Concawe 1997, Bascom et al 1996, WHO 1996, DoE 1996, DoE 1994, Health Canada 1995, USEPA 1992, USEPA 1991, Streeton 1990, WHO 1987, Environment Canada 1987, USEPA 1979, WHO 1979). In addition, both WHO 1979 and WHO 1987 recently have been revised but not yet published (Maynard 1996, 1997). There have been no significant variations in the approaches adopted by the various national and international jurisdictions to the adverse health effects of CO over this time, namely that to achieve adequate protection of the more susceptible population sub-groups (those with ischaemic heart disease; those with other forms of cardiac disease including cyanotic heart disease; hypoxaemic lung disease; cerebrovascular disease; peripheral vascular disease; those with anaemias and haemoglobin abnormalities; children; and the developing foetus), a carboxyhaemoglobin level of not more than 2.5% whilst either at rest or during active physical exercise should not be exceeded.

The linear relationship that exists between CO and haemoglobin ensures that predictable levels of COHb will be achieved for a given ambient concentration, for a given duration of exposure, and at a given level of rest or exercise. CO has the added 'advantage' in that unlike the other gaseous ambient pollutants, it has no interaction with lung tissues or structures but rather it diffuses directly across the alveolar membrane to combine with red cell haemoglobin within the pulmonary capillary network. As haemoglobin has some 220 times more affinity for CO than it does for oxygen, rapid transfer across the membrane and uptake by the red blood cells is assured, this uptake being enhanced by the increase that occurs in ventilation during exercise.

Over the past two decades, research has focussed on the characterisation of cardiac health effects in persons with ischaemic heart disease, a group regarded as the most sensitive to the adverse effects of CO.

Protection of this group has been the basis for the air quality standards that have been applied in jurisdictions around the world. The impact of even minor increases in COHb levels have been consistently demonstrated in both controlled exposure studies and in community epidemiological reviews, with the clear message that a reduction in community levels of exposure to CO should reduce the occurrence of ischaemic episodes and the consequent increase in risk for acute myocardial infarction. There is no valid evidence to support claims that CO exposure leads to the development of atherosclerosis, but rather that the atherosclerotic process results from, or is aggravated by, some components of tobacco smoke.

Healthy persons are unlikely to be significantly affected by ambient levels of CO with regard to possible limitation of exercise capacity, and neurobehavioural effects are unlikely at COHb levels of less than 15 - 20%.

Maternal smoking is well recognised as a significant cause of reduced birth weight and delays in foetal and neonatal development, and would appear to be reasonably attributed to CO exposure at levels of COHb between 2.0% - 7.0%.

These various adverse health effects are summarised in Table 1 of this Appendix.

Occurrence

Carbon monoxide (CO) is an odourless, colourless and tasteless gas. The bulk of atmospheric CO arises as a result of the incomplete combustion of carbonaceous materials, particularly fossil fuels. Other sources include natural gas, volcanoes, large fires such as forest or bush fires, and the metabolism of a number of organisms (especially marine organisms). CO is also produced endogenously in small quantities within the human body (of the order of 0.5% COHb equivalent daily) and, more recently, has been implicated as an important neurotransmitter for vasomotor control, possibly as important, if not more so, than nitric oxide.

At present, motor vehicle exhaust emissions are the source of the majority of urban production of CO. Currently in the U.K.(as of 1993), 90% of ambient CO emissions are from vehicles, 87% petrol, 3% diesel (DoE 1996). Most of the remainder comes from heavy industries such as steel mills and foundries, from the open burning of agricultural, domestic and commercial waste, from natural decomposition at refuse tips, and from the combustion of fossil fuels (coal and oil) generally. Major important and damaging indoor sources are tobacco smoking and open fires.

Under natural conditions, atmospheric CO levels are limited by chemical transformation of the gas in the stratosphere, and through its uptake both by micro-organisms in soil and water, and by plants.

Effects on Human Health

CO prejudices human health by reducing the amount of oxygen which can be carried in the blood to the body tissues. When CO is inhaled into the lungs, it combines selectively with haemoglobin (the oxygen-transport protein contained in the red blood cells) to form carboxyhaemoglobin (COHb). Haemoglobin which has been thus transformed is no longer available for oxygen transport, and as a result the brain, nervous tissues, heart muscle and some other specialised tissues which require large amounts of oxygen may not receive sufficient to function optimally, and may suffer temporary or permanent ischaemic damage as a result. High levels of exposure can cause acute poisoning, leading to coma and death at COHb levels of greater than 40%.These high exposures are fortunately rare, and occur either accidentally in poorly ventilated situations with combustion devices, deliberately as with suicide, or in the occupational setting as with fire-fighters, etc.

This review is restricted to the pathophysiological and toxicological effects of low level exposures to CO, such as occur in the context of ambient or indoor environments. The small amounts of CO which are normally produced endogenously occupy approximately 0.5% of the total haemoglobin content as COHb.

Tobacco smoking, both actively, and also passively when indoors, can lead to significant increases in COHb concentrations (of the order of 3.5% - 15%) , an effect which may be compounded in the urban environment by CO from other sources, notably motor vehicle emissions. These effects can be especially marked in certain situations of potential high exposure such as with police-officers and others on duty in busy streets, attendants in underground parking stations, in road tunnels (staff as well as vehicle occupants), and in other locations where dense traffic might be slowly moving or stationary with engines idling, and with poor ventilation.

In recent years, it has been increasingly recognised that the occupants of motor vehicles commonly demonstrate a significant increase COHb% compared to the ambient level of CO outside the vehicle. This finding has particular relevance in situations of high traffic density, usually in only slowly moving or stationary as in traffic jams, road tunnels, and similar situations.

It should be noted that if an individual has a COHb level which is greater than would be expected from the ambient background (for example, a heavy smoker), then that individual will act as a source or net emitter of CO rather than as a receiver of CO, thus the effects of smoking and exposure to ambient CO are not necessarily additive but need to be considered on an individual basis.

Under normal circumstances, CO produced by motor vehicles is generally dispersed rapidly away from roads, and then progressively destroyed by photochemical processes over some months. Atmospheric conditions can however interfere with this dispersal, such as might occur in conditions of still air with low level inversion layers during autumn or winter. In these situations, build-up of other pollutants such as nitrogen dioxide and respirable particles can also occur, compounding the individual adverse effects of each of the constituents.

The health effects of short-term acute CO exposures have been studied in many countries, either as controlled human exposure studies, as studies of longer-term exposures in populations, in animal studies or *in vitro* to describe and to determine mechanisms of toxicity. These health effects include cardiovascular effects on work/exercise capacity at normal and at maximal levels in healthy subjects and in subjects with known ischaemic heart disease; neurobehavioural effects including perception, manual dexterity, and the ability to learn and to perform complex tasks; and effects on the developing foetus. Table 1 of this Appendix summarises the currently published lowest observed effect levels (LOEL's), and no observed effect levels (NOEL's).

Extensive population studies suggest that healthy non-smokers living in clean rural environments have COHb levels of less than 1%, whereas healthy non-smokers in urban environments have between 1.0% and 2.0% COHb content depending on background concentrations of CO. No discernible

physiological or psychometric effects have been demonstrated at these levels.

At between 2.5% and 5.0% COHb content, there is evidence of an increasing incidence of angina pectoris, especially during exercise, in those with significant coronary artery disease. Above 3.0% COHb, there is also increasing psychometric dysfunction (a measurable increase in normal response time). COHb levels in average smokers (around 1 pack per day) far exceed these levels, ranging from 5% to 15% of total haemoglobin content, depending on their individual patterns of tobacco consumption.

Objective or guideline levels as recommended by various jurisdictions over the last two decades have been based on the assumption that exposure to ambient CO is unlikely to harm human health where it produces COHb levels of less than 2.5% total haemoglobin content (USEPA 1979; WHO 1979; WHO 1987). Subsequent research has confirmed this assumption (USEPA 1991; USEPA 1992; DoE 1994; WHO1995; Health Canada 1995; DoE 1996; Maynard 1996), finding no evidence to suggest that even the more sensitive individuals (non-smokers suffering from angina pectoris) are likely to suffer any significant harmful effects at this level (USEPA 1984a; USEPA 1984b; WHO 1987; Environment Canada 1987). In addition, air quality guidelines or objectives currently in place or as proposed revisions aim to ensure that neither smokers nor non-smokers will be exposed to levels of ambient CO which would result in blood COHb concentrations of greater than 2.5%, at any level of physical activity from the resting state through to maximal exercise.

Toxicological Mechanisms

The relationship between ambient levels of CO and the resultant COHb levels is complex. There are dilution effects in the body tissues, and it can take 10 - 12 hours following continuous exposure to CO for the blood COHb levels to achieve a steady-state equilibrium. Under conditions of increasing exercise, equilibrium is achieved more rapidly because of increased alveolar ventilation rates, increased gas exchange (diffusing capacity), and increased cardiac output. Even mild exercise increases the body's demand for oxygen, and thus can enhance the effect of exposure to a given concentration of ambient CO.

The rate of uptake of CO is initially dependent on the pre-existing back-pressure for CO. Rates of uptake are also affected by body size, with women and children having higher rates of uptake than do adult men. As ambient concentrations of CO are generally low, excretion of CO can be prolonged as the driving back-pressure (pulmonary capillary CO content) is very low. At normal resting ventilation levels, breathing room air at sea level, the half-life of CO in the blood is of the order of 2 - 4 hours, but this clearance is much affected not only by ventilation rates, but also by the ambient oxygen concentration or pressure (hence the value of hyperbaric oxygen for treating acute CO poisoning).

The relationship between CO and haemoglobin is linear at CO concentrations of up to 200 ppm. at sea level, and when exposed continuously, COHb% at equilibrium can be reasonably approximated by the relationship:

$$\textbf{COHb\% = CO(ppm) x 0.16}$$ (Bascom et al 1996).

As an example of the application of this relationship under steady-state conditions, if the currently accepted guideline/objective for a continuous 8 hour exposure of 9 - 10 ppm of CO is used, then COHb level in healthy nonsmokers cannot exceed 2%.

Whilst this relationship gives an estimate of COHb% at equilibrium, it does not allow for estimation of non-steady state COHb% at various durations of exposure, or at differing levels of exercise. Prediction formulae have been developed - in particular, the COBURN-FORSTER-KANE (CFK) exponential equation (Coburn et al 1965) - which take into account these variables and make it possible to accurately predict the COHb% which might result from exposure to a given ambient level of CO in the inspired air for a given length of time, at different levels of physical activity from rest through to maximal exercise. This relationship has since been validated in persons with healthy lungs at environmental levels of CO (Peterson & Stewart 1975). Allowance should also be made for the changes that take place in both the red blood cell haemoglobin and in muscle myoglobin oxygen transport and to oxygen uptake by muscles in the presence of an increased CO load. For further detail on the specifics of oxygen transport and the metabolism of carbon monoxide, the reader is referred to the reference texts detailed below, or to Coburn and Forman (1987).

ADVERSE HEALTH EFFECTS

Cardiovascular Effects

Healthy Individuals
Maximum oxygen consumption (VmaxO2) attained during progressive exercise testing has been the primary test end point in healthy individuals as the basis that any increase in COHb should reduce systemic oxygen transport, and thus maximal cardiac output. In a range of studies in healthy non smoking individuals, maximal exercise time and maximal oxygen consumption were found to be reduced in the presence of COHb levels as low as 5% (Pirnay et al 1971, Ekblom & Huot et al 1972, Vogel & Gleser et al 1972, Aronow & Cassidy 1975, Horvarth et al 1975, Klein et al 1980, Hirsch et al 1985). These reductions appear to be linear, with an approximately 1% reduction in VmaxO2 for every 1% increase in COHb above a threshold COHb level of 4%.

Normal healthy individuals have compensatory mechanisms which allow adjustment for reductions in tissue oxygenation such as increased cardiac output, and increased tissue perfusion. However notwithstanding these adaptive mechanisms, it has been demonstrated that the maximal exercise performance of healthy individuals can be affected by low levels of COHb, as low as 2.3 -4.3% in some studies (Drinkwater et al 1974, Raven et al 1974, Horvath et al 1975). There is no evidence to suggest that these small observed reductions in exercise capacity in healthy individuals will interfere with normal daily living activities.

It should be noted that the acute effects of tobacco smoking on maximal exercise performance are similar to those seen with CO exposure. (Klausen et al 1983, Hirsch et al 1985).

Individuals with Ischaemic heart disease
Certain medical conditions such as anaemia and arteriosclerotic vascular disease can increase an individual's potential for susceptibility to the adverse effects of CO exposure during exercise. Those individuals with ischaemic heart disease are particularly vulnerable as they are unable to increase coronary artery blood flow to a sufficient degree to satisfy increased myocardial demands for oxygen during exercise. Tissue hypoxaemia with subsequent ischaemia may then occur, resulting in chest pain (angina pectoris), together with ECG changes consistent with ischaemia.

Several studies reported by Aronow and co-workers (Aronow et al 1972, 1973, 1974, Aronow 1978, 1981) suggested that elevation of COHb levels by only 2 - 3% were sufficient to decrease the time to onset of exercise induced angina. However, these results were later seriously questioned (Horvarth et al 1983) on the basis of concerns relating to data collection and analysis, and have since been discounted.

The qualitative hypothesis of Aronow and co-workers that CO exposure can enhance the development of exercise-induced angina in individuals suffering from coronary artery disease has however since been confirmed in several subsequent studies. In particular, the studies undertaken by Allred and co-workers on behalf of the Health Effects Institute (Allred et al 1989a, 1989b,1991) demonstrated that in persons with documented coronary artery disease, effects of CO could be objectively demonstrated by observing ECG changes during exercise.

To summarise these studies, persons with known coronary artery disease were exercised, double-blind, on a treadmill, breathing either room air or one of two CO concentrations with levels of (a) 120 ppm and (b) 250 ppm respectively. Room air exposure resulted in COHb levels 1.2% before exercise and 1.4% after exercise. The two CO exposures resulted in COHb levels of (a) 2.6% before and 3.2% after; and (b) 4.7% before and 5.6%, and were found to be associated with a decrease in the length of time to a threshold ischaemic ST-segment change of

5.1% (p=0.01) and 12.1% (p≤0.0001) respectively. The length of time to onset of angina was also found to be decreased by (a) 4.2% (p=0.027) and (b) 7.1% (p=0.002) respectively.

Allred et al concluded in their various reports that low levels of COHb exacerbated myocardial ischaemia during graded exercise in persons with coronary artery disease. Other studies have also been reported demonstrating similar findings (Anderson et al 1973, Sheps et al 1987, Adams et al 1988, Kleinman et al 1989). Conversely, some more recent studies, again supported by the Health Effects Institute, have not demonstrated similar effects when individuals with known coronary artery disease have been similarly exposed to CO under exercise conditions (Sheps et al 1990b, Chaitman et al 1992).

The various clinical studies are summarised in Table 2 of this Appendix.

There is general, although by no means universal, support for the hypothesis that low COHb levels in the range of 2 - 6%, can result in small decrements in exercise performance in persons with exercise-induced ischaemia. There remains some debate however as to whether or not these small decrements are of clinical significance. Some would argue that these decrements are within the normal range of reproducibility for the exercise tests used in the studies. Others argue that these effects, if real, could limit the daily activities of affected individuals, and reduce their quality of life. (Mall et al 1985, Hinderliter et al 1989, Sheps et al 1990a).

In some other reported studies, it has been suggested that low COHb levels are related to exercise-induced arrhythmias, thus CO exposure might increase the risk of sudden death from induced arrhythmias in some individuals but this finding has not been not consistently confirmed (Dahms et al 1993).

A retrospective study on New York tunnel and bridge workers (Stern et al 1988) reviewed the deaths due to arteriosclerotic heart disease in these workers with those seen in the general New York population. 61 deaths were counted, as against 45 expected, giving a standardised mortality ratio of 1.35 (90% CI 1.09 - 1.68). There were differences seen within the study group, with twice as many tunnel workers as bridge workers (toll gate operators) being affected. The exposure to CO was also different for both groups, being ~50 - 150 ppm in the tunnels compared to ~12 - 45 ppm on the bridges and toll gate booths. It was also noted that following the introduction of improved ventilation into the tunnels and to the toll gate booths in 1970, there was a significant reduction in risk of death from ischaemic heart disease.

Several epidemiological studies have been reported (Hexter et al 1971, Kurt et al 1978, Kurt et al 1979, Lambert et al 1992, Morris et al 1995) however results have been conflicting, presumably on account of the difficulties in adjusting for

confounding factors such as tobacco smoking, and poor correlations between ambient CO monitors and personal monitors. However, a general conclusion can be made that chronic community exposure to CO may exacerbate heart disease, and that reduction in community CO exposures should reduce the frequency of myocardial ischaemia in persons with ischaemic heart disease, thus reducing the risk of fatal myocardial infarction.

Neurobehavioural Effects

Many studies have been undertaken to asses the effects of elevated COHb on visual perception, auditory perception, vigilance, motor skills, cognitive ability, and sensorimotor performance. Although initial early studies suggested possible neurobehavioural effects with COHb levels as low as 1.8%, these findings could not be reproduced by later workers, and have been discounted.

A wide range of COHb threshold levels have been reported as leading to disturbances in fine neurobehavioural function, in particular the ability to discriminate time intervals, and to perform complex motor and sensorimotor activities. No significant neurobehavioural effects have been described for COHb levels of less than 5%. Most reported threshold responses range between 5.0% - 7.6% COHb for a statistically significant reduction in vigilance, and between 5.0% - 17% COHb for the detection of statistically significant impairment of visual perception, manual dexterity, ability to learn, and the performance of complex sensorimotor tasks (Laites et al 1979, USEPA 1984a, Benignus et al 1987, USEPA 1992).

The associations between severe CO toxicity and marked effects on the central nervous system have been well described for both acute toxic exposure , and following chronic exposure. In the context of acute exposure, loss of consciousness leading to coma and death is well recognised. With chronic CO toxicity (at sublethal concentrations), chronic brain syndromes, mental retardation and Parkinsonian-like states are well recognised.

Suffice to say, major uncertainty remains as to whether or not subtle changes in neurobehavioural function result from exposure to concentrations of CO that yield only modest increases in COHb. More significant increases in COHb to between 15 - 20%, especially if more prolonged, can result in the development of headache although there is evidence to suggest that these headaches are more likely to be the result of cerebral compensatory mechanisms in response to relative cerebral hypoxia, leading to cerebral vasodilatation (Penny 1988). Cerebral tissue has been shown to become more efficient at oxygen extraction in the presence of tissue hypoxia, and in animal experiments, there are indications of good compensatory responses to cerebral blood flow until levels of COHb of the order of 30% are achieved.

In conclusion, it would appear that the effect of COHb levels below 5% on neurobehavioural function is negligible, and can for be disregarded in the context of normal daily living.

Foetal and Developmental Effects

Maternal tobacco smoking is well recognised as a significant cause of lower birth weight and increased foetal and neonatal mortality (Alderman et al 1987, US Dept. Health 1990), although precise mechanisms have yet to be described. Similar patterns of significant increases in foetal mortality have been described in animals such as the rat (Garvey & Longo 1978) It is possible that by interfering with maternal oxygen transport, the CO contained in tobacco smoke is able to contribute to these foetal effects.

Although foetal haemoglobin has a slightly lower affinity ratio for CO (180) compared to that for adult haemoglobin (220), studies of COHb levels in foetal cord indicate that foetal COHb levels tend to be increased relative to the COHb levels in maternal blood drawn at the same time from mothers who have smoked during pregnancy and labour (Bureau et al 1982). Animal studies have demonstrated similar patterns (Longo & Hill 1977).

The foetal central nervous system appears to be particularly susceptible to CO exposure, and maternal smoking during pregnancy has been suggested as a cause of delayed and possibly long term impairment of neurological and intellectual development (Longo 1977, USEPA 1979). Studies in rat embryos would support this hypothesis in that even modest levels of maternal smoking may render the foetus highly susceptible to irreversible neural impairment.

These effects have not been described for COHb levels of 2.0% or less, but are described for a range of threshold COHb levels from 2.0% - 7.0%. It should be noted that all reported studies appear to have been undertaken in the context of maternal smoking, although concerns have been expressed from time to time about the possible impact that passive exposure of non-smoking mothers to urban air as well as to the side-stream smoke from smoking mothers might have on their unborn infants. As yet, no clear trends have been described.

In summary, the foetus and newborn infant appear to be particularly susceptible to even minor increases in COHb levels above 2.0%, however as a public health issue, control of maternal tobacco smoking would appear to be the major protective measure required at this time.

PROTECTIVE CONCENTRATION RANGES

As indicated above, there has been universal agreement around the world that for adequate protection of susceptible populations, CO concentrations in ambient air (indoors or outdoors) should be such that no matter what duration of exposure or level of exercise activity, COHb concentrations should not exceed a recommended No Observed Effect Level (NOEL) of 2.5%.

In most jurisdictions, there has been a trend to establish air quality standards / guidelines / recommendations based not only on exposure periods by which equilibration will be achieved (8 hours or more), but also based on shorter periods to control for the potentially adverse effects of more intense but shorter-lived exposures. By use of the Coburn-Forster-Kane (CFK) equation, allowance can be made for the recognised physiological variables known to effect CO uptake by an individual, either healthy or compromised. In this way, periods of time-weighted average exposures and CO levels can be determined in order to ensure that the COHb level of 2.5% is not exceeded in any exposed individual, even when that individual is engaged in heavy manual work.

In developing suggested ranges for protective concentrations, not only is it necessary to provide protection for susceptible populations, especially those with ischaemic heart disease, it is also desirable to ensure that an appropriate safety factor is incorporated to protect the most sensitive groups of all, namely those identified as suffering from clinical angina. Using the CFK equation, it can be shown that in an individual at rest, the CO concentration producing a COHb level of 2.5% after 8 hours exposure is 15 ppm. It is usual public health practice to apply a safety factor of 1.5 times the NOEL , thus reducing the safe ambient CO concentration to 10 ppm.

At a concentration of 10 ppm, a continuously exposed non-smoking population would have COHb levels which should not exceed 1.6%. This relationship applies whether the individual is sedentary, or undergoing heavy physical activity. By basing the primary exposure standard / guideline on an 8-hour averaging time, there should be sufficient protection for the population as a whole against continuous lifetime exposures. By extrapolation, CO concentrations relating to shorter averaging periods can also be estimated, including a safety factor, even although at these shorter exposures, equilibrium through the various body compartments will not have been achieved. These shorter averaging period guidelines are especially important in situations where there is potential for more intense exposure, such as in dense slow-moving traffic in street canyons, in tunnels, in underground or enclosed carparks, etc.

A review of recommended standards / goals / guidelines from around the world indicates universal acceptance of an eight (8) hour exposure standard of 9 – 10 ppm, with shorter term one (1) hour exposure standards ranging between 25 - 30 ppm (the differences mainly relate to the use of differing correction factors for temperature at atmospheric pressure). Current standards

/ guidelines here in Australia (NHMRC and State) all conform closely to international standards / guidelines.

More recently, WHO (1995) has indicated in draft guidelines yet to be published that additional shorter term guidelines to protect for more intense, but short-lived exposures, such as might occur in enclosed situations such as tunnels, etc., should be considered. These shorter term guidelines include
(a) 90 ppm for a 15 minute average exposure period, and
(b) 50 ppm for a 30 minute average exposure period.

In the Australian context, it is our impression that the 1-hour and 8-hour standards are rarely, if ever, exceeded in Australian cities, with the one exception of Sydney where a number of exceedances have been recorded each year over the past several years.

TABLE 1

	Carboxyhaemoglobin (COHb) Note that exposure averaging times are not specifically applicable as effects relate to COHb levels rather than to duration of exposure (see text).	
	Lowest OEL	**No OEL**
CARDIOVASCULAR EFFECTS		
Healthy Young Adults		
Decreased O2 Uptake	5.0% - 5.5%	<5.0%
Decreased Work Capacity (Maximal Exercise)		
Significant Decrease in Work Time	3.3% - 4.2%	<3.0%
Strenuous Exercise – Reduced Maximal O2 consumption	7% - 20%	
Ischaemic Heart Disease		
Decreased Exercise Capacity	2.9% - 4.5%	2.5%
At Onset of Angina		
Increased Duration of Angina		
NEUROBEHAVIOURAL EFFECTS		
Healthy Adults		
Statistically Significant Vigilance Decrements	5.0% - 7.6%	<5.0%
Statistically Significant Diminution of Visual Perception, Manual Dexterity, Ability to Learn, Performance of Complex Sensorimotor Tasks	5.0% - 17.0%	<5.0%
FOETAL EFFECTS		
Reduced Birth Weight (Non Smoking Mothers)	2.0 % - 7.0%	<2.0%

TABLE 2

**Summary of Studies on the Cardiorespiratory Effects of Carbon Monoxide
on subjects with Ischaemic Heart Disease.**

Study	Subjects	COHb Levels	Effects
Anderson et al. (1973)	• 10 males, 5 smokers, and 5 non-smokers, with reproducible exercise-induced angina, average age 50 years • air, 50 ppm CO, or 100 ppm CO for 4 hours on 5 consecutive days; post exposure exercise on a treadmill	• COHb levels after CO exposure 2.9% (50 ppm CO) and 4.5% (100 ppm), from baseline level of 1.3%	• Duration of exercise before onset of angina significantly shortened after exposure to 50 and 100 ppm C0 ($p < 0.005$); time to onset of angina decreased by about 21% in both exposure groups • Duration on angina increased significantly only after exposure to 100 ppm C0 compared with air ($p < 0.01$) • No difference between smokers and non-smokers • ST segment depression occurred earlier and was deeper after exposure to CO
Sheps et al. (1987)	• 30 non-smoking patients, aged 38-75, with ischaemic heart disease • 100 ppm CO for duration necessary to achieve COHb level of 4%; post-exposure incremental exercise at 317 kpm on a cycle ergometer	• Average COHb level 3.8% (CO-0x), 2.2% increase over baseline	• No difference in time to onset of angina, maximal exercise time, maximal ST depression, time to significant depression in ST, resting injection fraction, or maximal injection fraction • Change in ejection fraction slightly lower following by exposure to CO
Adams et al. (1988)	• 30 non-smoking patients (aged 36 - 75) with evidence of exercise induced angina • 100 - 200 ppm CO for 60 min; post-exposure incremental exercise at 300 kpm on a cycle ergometer	• COHb level after CO exposure 5.9% (CO-Ox), 1.6% increase over baseline	• Mean duration of exercise significantly shorter ($p < 0.05$), angina more likely to be experienced earlier during exercise ($p < 0.05$), and level and changing in left ventricle injection fraction at submaximal exercise lower (both $p < 0.05$)
Allred et al. (1989)	• 63 male non-smokers with exercise induced angina, aged 41 to 75 • 117 or 253 ppm CO (means) for 50 - 70 min; pre- and post-exposure incremental exercise at about 6 METs (basal metabolic equivalents) on a treadmill	• COHb levels after CO exposures: 3.2% and 5.6% (2.0% and 4.4% above baseline) (CO –Ox); 2.4% and 4.7% (1.8% and 4.O% above baseline) (GC) • COHb levels after exercise test; 2.7 and 4.7% (CO – Ox); 2.0 and 3.9% (GC)	• Decrease in length of time to threshold ischaemic ST-segment change of 5.1% ($p = 0.01$) and 12.1% ($p < 0.0001$) • Length of time to onset of angina decreased by 4.2% ($p = 0.027$) and 7.1% ($p = 0.002$) • Significant linear dose-response relationship for time to ST change
Kleinman et al (1989)	• 24 male non-smokers with reproducible exercise-induced angina, 49 -66 years • 100 ppm CO for 60 min; post-exposure incremental exercise at 48.6 L/min on a cycle ergometer	• COHb level after CO exposure 3.0%, 1.5% increase over baseline	• 3% reduction in oxygen uptake at angina ($p = 0.04$) and 6% reduction in time to onset of angina ($p = 0.046$) • 12% reduction in time to onset of angina and 20% reduction in time to onset of 0.1 mV ST segment depression in subset of individuals who exhibited depression in the ST segment

Study	Subjects	COHb Levels	Effects
Sheps et al. (1990b)	• 41 subjects (nonsmokers) with documented coronary artery disease; 16 never smoked, 25 previous smokers; average 63 years, 5 females and 36 males	• 100 ppm CO, 200 ppm CO supine bicycle exercise test • COHb level after exposure 4.0%, increase 3.2% over baseline. • COHb level 5.9% after exposure, increase 5.1% over baseline.	• Frequency of a single premature ventricular contractions per hour during exercise was significantly greater at 6% COHb; frequency of multiple premature ventricular contractions per hour was significantly greater during exercise with 6% COHb; patients developing increased arrhythmias during exercise at 6% COHb were significantly older, exercised longer and had a higher peak workload during exercise. No effect of CO seen at 4% COHb
Chaitman et al. (1992)	• 30 Subjects with documented ischaemic heart disease; 25 males, 5 females; average age 65 years	• Two CO levels: 150 minute exposures, 2 minute interval walks, increasing workload by 1 MET each stage, maximum workload 11 METs • 3.2% and 5.1% COHb levels after exposure; increases of 2.5% and 4.5% respectively	• No increase in ventricular arrhythmia frequency after exposure; frequency of complex ventricular ectopy was not altered

Adapted from Health Canada (1995), and Concawe (1997).

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APPENDIX 2 -
HEALTH EFFECTS OF LEAD

SUMMARY [#]

The earliest recognised effect of lead exposure is a decrease in intelligence and general academic performance in children resulting from exposure within the first 2-3 years of life. There is now clear epidemiological evidence of a close causal relationship between prenatal exposure to lead (as measured by umbilical cord blood) and early mental development indices.

This effect has been attributed to lead present at blood levels as low as 10 μg/dL, but the absence of any identifiable threshold level suggests that a deleterious effect may be produced by blood lead levels lower than 10 μg/dL (< 0.48μmol/L). Lead may exert its effects by substituting for calcium in critical biochemical reactions.

Recent studies have raised the possibility that low levels of lead may increase blood pressure in adults. This may increase the risk of stroke and coronary artery disease over a population with consequent increases in both morbidity and mortality. The statistical significance of these observations is however low at this time (not more than 5%).

Regulatory agencies in the United States, Canada, Australia and elsewhere have developed policies to reduce blood levels of lead to 10 μg/dL or less (not greater than 0.48μmol/L) for all of their populations, from the youngest to the oldest although clearly some groups are at more potential risk for adverse effects from lead than are others. Table 3 later in this review sets out in summary the various adverse health effects that have, thus far, been identified as causally related to lead.

In countries where lead is used as a petroleum additive, the majority of airborne lead in urban areas (at least 75%, and probably greater in some situations) is derived from this source. Airborne lead levels of up to 10 μg/m³ have been measured near areas of high traffic density. After the removal of leaded petrol, airborne levels in urban areas commonly fall to below 0.2 μg/m³.

At present the major routes for lead intake for both children and for adults are by inhalation and by ingestion. Lead particles emitted from vehicle exhausts fall into the 'fine' (less than 2.5 μm) and 'ultra-fine' (less than 1.0 μm) fractions, and as such, are readily inhaled and deposited in the respiratory tract. Ingestion of dust or soil containing deposited lead particles also makes a major contribution to the intake of lead in young children who live near major roads or near point sources (smelters, etc) of lead exposure where extensive deposition of lead in

[#] Reviewed and edited by Dr. Jonathan Streeton, FRACP.

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Prepared by Dr Jonathon Streeton for the National Environment Protection Council

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soil has occurred. Unlike other exposure sources which are declining, contaminated soil and dust are likely to remain as important exposure sources well into the future.

Airborne lead is a potentially important exposure source because of the relatively high levels of systemic absorption from the lungs. There is good evidence to suggest that of the order of 75% of inhaled fine particulate lead is absorbed from the airways, and is thus available for metabolism. However, absolute air levels are falling sharply in areas where restrictions on leaded petrol have been introduced. Apart from those individuals living near point sources of exposure, airborne lead levels can be expected to contribute decreasingly to the overall lead burden as the proportion of leaded petrol consumption falls in relation to total fuel sales.

The present air standard for lead exposure (1.5 $\mu g/m^3$ as a rolling quarterly mean) was established at a time when the detailed knowledge of the adverse effects of lead on the developing nervous system was less advanced. Continuous inhalation of air containing this level of lead would be expected to raise blood lead levels by between 1.5 - 3.0 $\mu g/dL$. Considering the present philosophy of attempting to maintain blood lead levels as low as possible, a strong case can be made for revising this standard downwards, perhaps to 0.3 $\mu g/m^3$. The indicator of outcomes would be by high volume air sampling, and in some circumstances lead levels in dust. For individual exposures, direct blood lead estimation remains the most appropriate method.

In conclusion, it is suggested that in order to establish an optimum ambient concentration for airborne lead so that appropriate protection from the adverse health of lead can be achieved for the whole population, ambient lead levels should be held in the range of 0.3 - 0.5 $\mu g/m^3$ on a mean moving monthly (or as an annual) standard, but NOT to exceed 0.5 $\mu g/m^3$ at any time.

Therefore a national standard or guideline of 0.5 $\mu g/m^3$ as a moving monthly mean, not to be exceeded, and reviewed not more than every five (5) years would appear to be the proper approach in 1997. Ambient levels of this order should adequately protect the range of risk groups in the community, from unborn foetuses, infants, and young children through to the general adult population.

TOXICOLOGICAL REVIEW [#]

Background

Lead is a metallic element which is present naturally in low concentrations in the earth's crust. It shares some chemical similarities with calcium and zinc and may exert at least some of its toxic effects by interfering with or substituting for these elements in key biochemical processes. Lead raises intracellular calcium levels and binds to several calcium-activated proteins with approximately 100 thousand times the affinity of calcium.

Lead has been used by humans for thousands of years. During the Roman Empire, it was used widely in water pipes, linings, aqueducts and food and drink utensils. Concentrations of lead in air, water and foodstuffs have risen since the onset of industrialised society. The magnitude of this increase is demonstrated by the fact that the whole-body lead content of modern North Americans is approximately three hundred times that of North American Indians prior to European settlement (Ericson et al 1991; Patterson et al 1991).

World production of lead is now estimated to average about 5.5 million tons, most of which is now used for the production of batteries, metal piping, metal solder, roofing and radiation shields. In the past, a large proportion of the lead produced was used for petrol additives and to a lesser extent in paints and ceramic products but these uses are now declining.

Environmental Origins of Lead

The origins of environmental lead are shown in Table 1 of this Appendix. Atmospheric emissions refer to fine particles which enter the atmosphere and which may be carried for great distances before settling onto soil. Although it is estimated that 80 percent of lead released into the atmosphere is deposited near the source, about 20 percent is widely dispersed. Air is the principle medium for the transport of inorganic lead in the environment. Analysis of the isotope content of airborne lead in remote areas of the world indicate that most of the lead present is derived from human activity.

In countries where leaded petrol was available, 80-90 percent of the lead in urban air was derived from this source. Exhaust fumes from vehicles using leaded petrol contains lead (principally as halides and oxides) in concentrations up to 24 mg/m^3 (Dzubay et al 1979). Less than 10 percent consists of organic lead compounds that have escaped combustion.

[#] Toxicological Review prepared by Professor J. McNeil, Dept. of Epidemiology and Preventive Medicine, Monash University, and edited by Dr. J. Streeton.

Air levels of lead in urban areas vary according to such variables as traffic density, proportion of vehicles using leaded petrol, the distance from major roads and prevailing weather conditions. In cities where leaded petrol was used widely, air levels ranged from 0.3 to 10 μg/m^3 and even higher levels were often encountered in confined areas such as garages. When leaded petrol was no longer available, air levels commonly fell to less than 0.2 μg/m^3 (Elias 1985).

Airborne lead levels are also likely to be high in the vicinity of point sources such as lead smelters and large refuse incinerators. Much of the lead emitted from these sources precipitates from the atmosphere within 1-2 km of the source.

Since most inorganic lead compounds are insoluble, then the lead deposited on soil generally remains localised to that area. In countries where leaded petrol was available, 80-90 percent of the lead in urban air was derived from this source. Exhaust fumes from vehicles using leaded petrol contains lead (principally as halides and oxides) in concentrations up to 24 mg/m^3 (Dzubay et al 1979). Less than 10 percent consists of organic lead compounds that have escaped combustion.

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TABLE 1

Sources of environmental lead (000 tons/yr) * (adapted from WHO 1995)	
(a) Atmospheric emissions	
petroleum additives	248
coal and oil combustion	3-18
metal smelting	31-83
refuse incineration	2-3
natural sources	20
other	5-22
TOTAL	290-380

(b)	Emissions into soil	
	atmospheric fall-out	200-260
	mine tailings	130-390
	smelter waste	190-390
	wastage of commercial products	200-390
	ash	45-240
	urban refuse	18-62
	TOTAL	800-1800

* figures from 1983-currently less than one third this amount is believed to be released from petroleum additives.

Pathways to Human Exposure

The pathways leading from the release of lead into the environment to its uptake by humans are summarised in Figure 1.

Airborne Lead

Environmental spread of lead takes place largely through the dispersion of airborne particles (Bates 1994). In most urban areas where leaded petrol is used, 80 - 90 percent of airborne lead is derived from the combustion of tetramethyl- and tetraethyl-lead in petrol. In areas within several kilometres of important point sources such as lead smelters the majority of airborne lead may originate from these sources.

Airborne lead eventually settles onto soil or vegetation and contributes to a large proportion of the oral intake. High soil lead levels occur throughout urban areas in close proximity to roads with high traffic volumes, close to point-sources such as smelters and close to structures coated with poorly maintained lead based paints. Dust originating from contaminated soil contributes principally to the oral (gastrointestinal) intake of lead and is a particularly important source in young children. Airborne lead deposited on soil is also transferred into the food-chain by uptake into food crops and by its adherence to leafy vegetables.

With the phasing out of leaded petrol, airborne lead levels have been shown to decline and, with time, this leads to a reduction in exposure from other sources. However, smaller numbers of individuals may continue to be exposed to airborne lead because of their proximity point-sources (such as smelters, incinerators or battery manufacturers) or from activities such as old-home renovations or the sand-blasting of lead-painted structures (CDC 1991).

Figure 1*
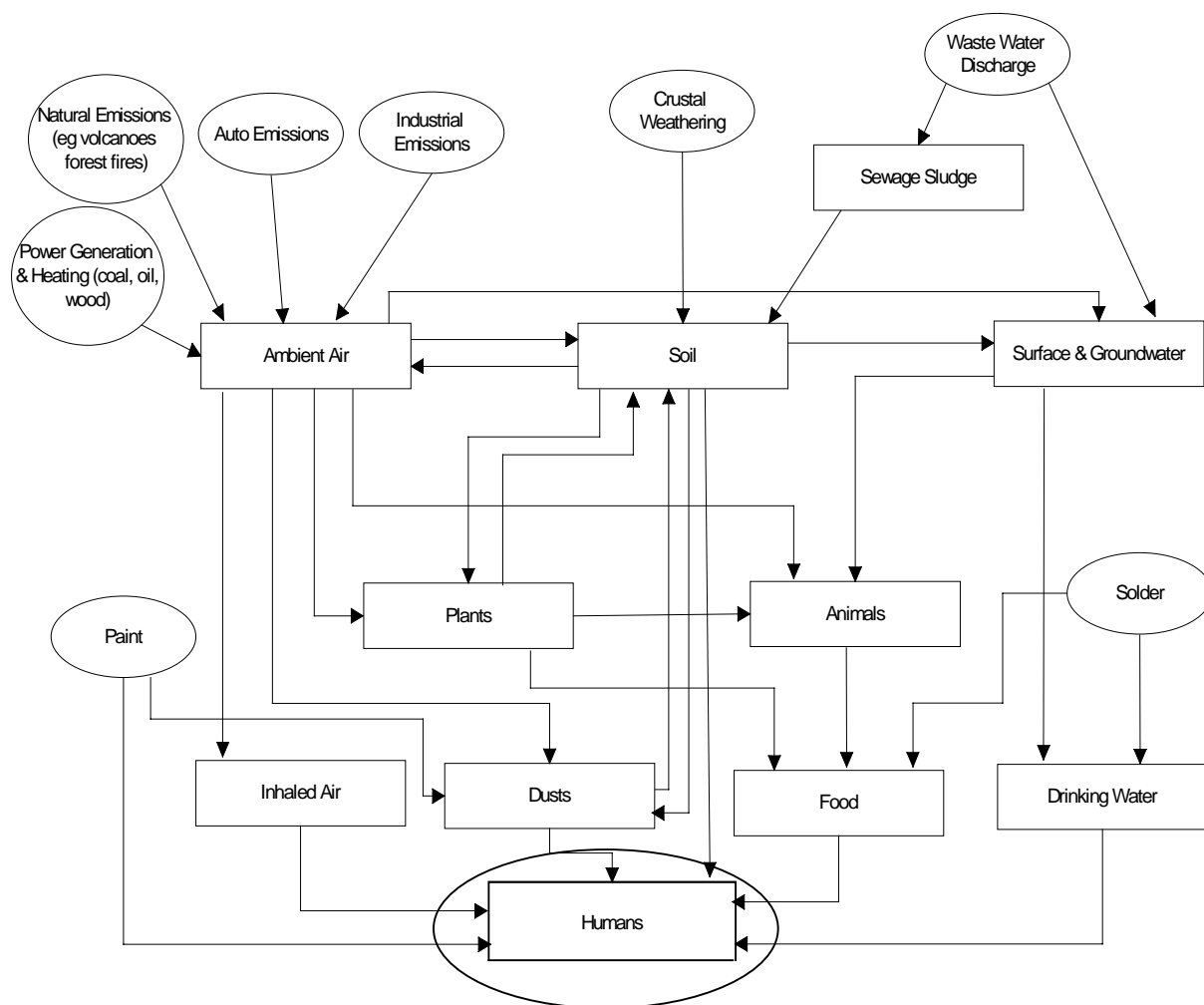
* Pathways of human exposure (OECD 1993)

Food
Food provides the largest proportion of the daily lead intake in most adults. The most important source is thought to be through the precipitation of atmospheric lead onto the foliage of plants. Foodstuffs produced in some urban 'home gardens' may be particularly affected (WHO 1995).

Lead concentrations in various food items are highly variable but have generally been falling in recent years. The average lead intake in the diet of adults has fallen from values of 100-500 μg/day in the early 1980's to a present value of 100 μg/day or less. The intake in young children is approximately half the adult intake. This reduction has been attributed principally to restrictions on the use of lead solder in cans, and on the reduced use of leaded petrol.

Average Australian dietary lead intake for 1-3 year olds in 1977 was estimated to be 156 μg/day, reducing to an average 26 μg/day by 1990 (source:

Australian 'market basket' survey 1990). These surveys have thus demonstrated an almost 50% reduction in lead intake for adults and 12 year old children, and a decrease in lead content of individual foods from 1977 to 1990 especially for canned foods. Although Australia has not regulated on the use of soldered cans, it was one of the first countries in the world to adopt welding of cans, and only welded cans are used for infant foods. The Australian 'market basket' survey (1990) found that 88% of cans produced in Australia were welded, and subsequently the Western Australia Canneries Survey (1992) found that 95% of cans produced in Australia were welded and only 5% soldered. The Australian Foods Standards Code (1987) specifies maximum permitted lead concentrations in food. These range from 0.2 - 2.5 mg lead per kilogram of food depending on the food type. The National Food Authority objective is 1.5 mg/kg for as many foods as possible.

Occasionally high dietary intakes may still occur from the use of herbal or traditional remedies, imported canned foods or through the storage of acidic foods in ceramic containers with improperly applied leaded glazes. In Australia, imported canned foods are unlikely to be a problem as AQIS rigorously monitors food lead in imported products.

Water

Lead concentrations are low in most ground and surface waters although they may increase as a result of contact with lead in the distribution system. The most common source of lead is in solder used to join copper pipes, although some very old houses may have residual lead piping. Except in unusual circumstances, water is believed to provide only a small fraction of the daily intake of lead (CDC 1991).

In 1977 water contributed to 6% of Australian dietary lead intake. A recent survey of Australian water supplies showed all levels to be less than 50µg/L (Commonwealth Environment Protection Agency, 1992).

Dust

The lead content of dust may be a major source of exposure to lead, especially for young children who ingest it when mouthing their hands, toys or food. Soil and dust may contain lead deposited from leaded petrol and lead paint and a variety of other sources. For example, levels of 10 mg of lead per gram of soil have been measured in soil adjacent to major roads (US EPA 1986). In soils close to lead smelters, lead levels of 130 mg/g of soil have been identified whilst the soil surrounding houses from which exterior lead-based point has been removed may contain between 2 and 370 mg/g of soil (Schlag and Flessel 1993).

Since lead compounds do not degrade and are slow to disperse, contaminated soil becomes a long-term source of lead exposure for children. Although dust

derived from the soil may be either ingested or inhaled, ingestion appears to contribute the major part of a child's intake. Methods of limiting exposure in high risk areas (which involves strategies such as top-soil replacement, and grass or bark chip cover) will require continuing attention for many years.

TABLE 2
Estimates of lead (μg/day) absorbed by adults and children
from air, dust, food and water *

Mean air lead concentration (μg/m³)	Dust intake (mg/day)[b]	Source of lead (μg/day)				Total absorbed (μg/day)	Predicted blood level (μg/d)	% of total intake from air
		Air	Dust	Food	Water			
Adults								
0.3	N.S.	2.4	-	10	2	14.4	5.4	17%
0.5	N.S.	4.0	-	10	2	16.0	6.0	25%
1.0	N.S.	8.0	-	10	2	20	7.5	40%
2.0	N.S.	16.0	-	10	2	28	10.5	57%
Children 1-5 yrs								
0.3	-	0.6	-	25	5	30.6	9.15	1.6%
0.5	-	1.0	-	25	5	31.0	9.3	3.2%
1.0	-	2.0	-	25	5	32.0	9.6	6.3%
2.0	-	4.0	-	25	5	34.0	10.2	11.7%
1.0	25	2	12.5	25	5	44.3	13.3	4.5%
1.0	50	2	25.0	25	5	57.0	17.1	3.5%
1.0	100	2	50.0	25	5	82.0	24.6	2.4%
1.0	200	2	100.0	25	5	132.0	39.6	1.5%

Adapted from IPCS (1995): Dust is not considered a significant source of lead in adults, but is a significant source for workers where hygiene practices are poor.

[b] N.S. = Not significant

The above estimates are based on the following assumptions:

Air: Respiratory volume in adults is 20 m³/day, and in children 5 m³/day, and the respiratory absorption is 40%.

Food: Intake of lead by adults 100 μg/day with 10% absorption and 50 μg/day for children with 50% absorption.

Water: A lead concentration of 20 μg/litre, with adult consumption of 1 litre/day and 10% absorption and for children 0.5 litre/day with 50% absorption.

Dust: Dust concentration of lead was 1000 μg/g and absorption was 50%.

Miscellaneous sources

Lead is present in tobacco smoke at low concentrations (approximately 2-12 μg/cigarette) and about 2-6 percent of this is inhaled (US EPA 1986). Substantial intakes of lead may also be derived from ceramic tableware, leaded

crystal glass, some traditional medications, some forms of calcium supplements and wines stored in bottles with lead foil covers.

In practice, air levels of lead are likely to be a mixture of fine and ultra-fine respirable particles (less than 1μm) which are inhaled, together with larger non-respirable particles which are deposited in the upper airways, swallowed and thus subsequently contribute to the ingested fraction of lead intake. In adults, the low extent of gastrointestinal absorption will make only a negligible contribution to blood lead levels from the ingested component. However the higher fractional absorption in children will cause the ingested component to contribute to blood lead levels in a similar fashion to adults. Assuming 50% absorption, the contribution would be similar to that seen if it were to be fully inhaled.

The biokinetic models used to predict mean blood levels are also useful for predicting frequency distributions of blood lead levels within a given population. In a simulation by Derosa et al (1991), the model was based on a US survey of blood lead levels (NHANES II, EPA 1986) and used a geometric standard deviation of 1.42 μg/dL. The subsequent probability distribution predicted for 2-3 year old children had a mean level of 2.98 μg/dL and 2 percent of children had levels exceeding 10 μg/dL.

Airborne Lead Levels

In remote areas such as the Antarctica concentrations of lead in air are commonly less than 10^{-4} μg/m³. (Maenhiaut et al 1979). At the other end of the spectrum are levels over 10 μg/m³ found in the vicinity of lead smelters (Elias 1985). Lead in air is generally bound to fine particles which vary according to their source. In urban areas, where the majority of airborne lead originates from motor vehicle exhaust, lead containing particles are usually less that 1μm in diameter. (US EPA, WHO 1987).

In cities where leaded fuel is still in use airborne concentrations of lead commonly range from 0.5 to 3.0 μg/m³. In Mexico, a city of particularly high traffic density, levels ranging from 0.6 to 5.7 μg/m³ have been reported (GEMS 1985). Following legislative action to reduce the lead content of fuel, urban air lead levels in the US fell to less than 0.07 μ/m³ (Elias 1985). Reductions of airborne lead have also been seen in Canada, Germany, Norway and the UK (OECD 1993).

Airborne lead levels are also high in the vicinity of lead smelters. In one study they were found to range from over 10 μg/m³ adjacent to the plant to 1.5 μg/m³ one kilometre distant (Wang et al 1992). These levels can be reduced by stringent emission controls.

In the absence of lead painted surfaces or other sources of indoor lead, the concentrations of lead inside a home is closely correlated with the levels outside (but only about 60% as high) (Davies et al 1987).

Dust Levels

Several studies have demonstrated a correlation between blood lead levels in childhood and lead levels in dust within and around the home (Robinowitz et al 1985, Bornschein et al 1987, Davies et al 1987, Laxen et al 1981, Steenhout 1987). The majority of the lead originates from deposition of airborne lead particles. In urban areas these come principally from fuel combustion or from the peeling and flaking of lead based paint. High levels may also originate from paint sources such as smelters (see previously).

Typical lead levels in road dust in the US range from 800-1300 mg/kg in rural areas to 100-5000 mg/kg in urban areas (US EPA 1989). Individual samples may contain as much as 10-30 gms/kg (WHO 1995). Lead based paint chips contain 1-5 gm/kg and dust levels are greatly increased after house renovation.

Contribution of Air Levels as a Proportion of Total Exposure

Estimates of lead intake in adults and children exposed to various concentrations of lead in air, dust, food and water have been developed by WHO (1995). Table 2 of this Appendix sets out estimates of proportional lead uptake from the different sources.

When air levels are of the order of 0.3 μg/m^3 (and other exposures are typical of current practice), the 2.4 μg of lead absorbed from this source contributes approximately 16% of the total intake (of 14.4 μg/day). With an increase in air levels to 1.0 μg/m^3, this proportion increases to 40% of a total intake of 20 μg/day.   In children, an air level of 0.3 μg/m^3 provides about 1.6% of total daily intake and an air level of 1.0 μg/m^3 provides about 6%.

Blood Levels in Australia

Over the last decade, there has been much local interest in determining the extent of lead exposure in Australia, with particular emphasis on current patterns childhood blood lead levels. Several reviews have been undertaken which examine community lead levels, exposure patterns and risk factors in considerable detail (Berry et al 1993; Edwards-Bert et al 1993a, 1993b; Donovan et al 1996). There is already clear evidence of a very significant improvement in the overall patterns of lead exposure in Australia, with now over 90% of Australian children (Donovan et al 1996) having blood lead levels of less than the current NHMRC guideline (NHMRC 1993) of 10 μgm/dL (< 0.49 μmol/L) .

In a recent meta-analysis, Stone (1997) has confirmed these patterns in Victorian children, with nearly 95% of childhood blood lead levels already being within the NHMRC guidelines. An exponential trend analysis performed as part of this study suggests that by 1993, a low estimate for national mean blood lead levels in children was already of the order of 0.3 µmol/L., and with long-term projections to 2005 of the order of < 0.2 µmol/L. Stone found that residual lead paint, rather than inner city living or proximity to heavy traffic (> 5000 vehicles/day), remained the major continuing general risk for young children at this time. Social factors also clearly play a considerable part in determining lead exposures and their consequent long-term health outcomes, and must be addressed in conjunction with other strategies to mininise childhood lead exposures (Donovan 1996).

Air Levels in Australia

The air quality standard adopted in both the US and Australia (excluding NSW where the standard is 1 µg/m³) has been 1.5 µg of lead per cubic metre of air as a rolling quarterly average. Prior to 1975 lead in Victorian petrol was 0.8 grams per litre, however this had been progressively reduced to 0.2 grams per litre by 1995. Currently 90% of airborne lead in greater Melbourne air comes from leaded petrol and 10% from industrial sources. In 1994 petrol sales showed unleaded petrol made up around 50% of total petrol sales. However, by the year 2000 it is anticipated that leaded petrol will only account for 10-15% of total petrol use.

The Victorian State Environment Protection Policy (The Air Environment), 1981 considered, on the basis of information available at the time, that a safe level of lead in air was 1.5 µg/m³ as a moving monthly mean. This standard has since been reviewed (Streeton 1990), and EPA Victoria subsequently recommended that this limit should be reduced to 1.0 µg/m³ as a moving monthly mean and adopted as a national standard in line with the recommendations from WHO (WHO 1987). By 1992, EPA monitoring of airborne lead in Melbourne and Geelong demonstrated lead levels generally less than, but not usually more than 1.0 µg/m³, this reduction being achieved as the leaded petrol car fleet is slowly but steadily replaced.

The relative contribution of airborne lead to the total daily lead intake has been estimated using the assumption of a 20 cubic metres/day respiratory volume in adults; 5 cubic metres/day volume in young children and with a fractional respiratory absorption in both age groups of the order of 40 percent (Table 2 in this Appendix). At a mean air level of 0.3 µg/m³, airborne lead contributes approximately 17 percent of total intake in adults and 2 percent in young children. This rises to 57% in adults and 12% in children at mean air levels of 2.0 µg/m³.

More recent appreciation of the neuropsychiatric effects of low level lead exposure and the goal of maintaining all Australians with a blood lead level at below 10 µg/dL suggests that the ambient air quality goal will require revision

downward. As leaded petrol is phased out, a new standard (goal or guideline) of between 0.3 to 0.5 μg/m³ based on a mean monthly or annual average would be appropriate and should provide for a feasible optimum level of protection not only for young children in particular, but for the population as a whole. Experience overseas indicates that when leaded petrol is phased out from a community, airborne lead levels of this order are not only achievable, but are readily attained.

Drinking Water Levels

The relative contribution of lead in drinking water to total lead exposure is usually low. In the United States, lead levels in drinking water are regulated by the US EPA. Lead and copper standards were first promulgated in 1991. Under the lead standard, an action level of 15 μg/litre of water was established based on first-draw samples taken at consumers taps. Action is required if at least 90% of samples are below the action level.

The current Australian (NHMRC 1987) guidelines for lead in drinking water were 0.05 mg/L, however this guideline has since been amended (NHMRC 1996) to 10 μg/L consistent with the current WHO guideline.

Benefits of Reducing Lead Exposure

The costs associated with exposure to lead amongst children result principally from the reduction in intellectual function which is presumed (on the basis of present evidence) to continue into adult life. These have been estimated by Schwartz (1994b). The shift in the distribution of intelligence levels, when summed across millions of children, can be predicted to produce a substantial increase in the numbers requiring special assistance. Lyngbye et al (1990) reported that children with elevated dentine lead levels (above 16 ppm) were over four times more likely to have a learning disability than those with lower levels.

In adults the continuing reduction of intellectual performance is likely to reduce average earnings, to reduce the quality of the home rearing environment for subsequent children and to result in a higher percentage of those with reduced work force participation (and reliance on Social Services). Adults may also be affected by higher risks for myocardial infarction and for stroke as a consequence of elevated blood pressure. Table 3 in the Appendix presents in summary a review of the major adverse health effects attributed to lead in both adults and children, and the various blood lead levels that have been described as being associated with these various adverse health effects.

Combining these estimates, Schwartz (1994b) estimated that every decrease of 1 μg/dL in the average blood level produced total savings (that is, reduced cognitive damage, reduced foetal effects, reduced effects on blood pressure

and cardiovascular disease) of the order of 17 billion dollars (US). Whilst there is a considerable element of speculation in these figures, they indicate that the costs of lead abatement and consequent reduction in health costs may produce substantial long term gains.

In Australia, Berry et al (1993) reviewed the Australian situation, undertaking both a risk assessment, and an analysis of the economic, social and environmental impacts of lead exposure. A series of recommendations for a national strategy were made, including dissemination of guidelines to health professionals, reviewing current ambient lead levels, lowering of limits for lead in petrol, development and implementation of programs for home renovations and the recommendation of safe techniques, identification of housing at high risk for lead-based paints, and a number of other related strategies. Significant long-term community health benefits were envisaged.

TABLE 3
Summary of Lowest Observed Lead-induced Health Effects in
Adults and Children. *

Blood lead level (µg/dL)	Health Effect
> 100	Adults: Encephalopathic signs and symptoms
> 80	Adults: Anaemia Children: Encephalopathic signs and symptoms, chronic nephropathy (eg. aminoaciduria)
> 70	Adults: Clinically evident peripheral neuropathy Children: Colic and gastrointestinal symptoms
> 60	Adults: Female reproductive effects. CNS symptoms (ie. sleep disturbances, mood changes, memory and concentration problems, headaches)
> 50	Adults: Decreased haemoglobin production, decreased performance on neurobehavioural tests, altered testicular function, GI problems (ie. abdominal pain, constipation, diarrhoea, nausea, anorexia) Children: Peripheral neuropathy
> 40	Adults: Decreased peripheral nerve conduction, chronic nephropathy Children: Reduced haemoglobin synthesis and Vitamin D metabolism
> 25	Adults: Elevated erythrocyte protoporphyrin levels in males
15 - 25	Adults: Elevated erythrocyte protoporphyrin levels in females
> 10[a]	Adults: Elevated blood pressure (males aged 40 - 59 years) Foetus: Preterm delivery, impaired learning, reduced birth weight, impaired mental ability
≤ 10[b]	Children: Both the level of concern and the lowest observed adverse effect level (LOAEL) for the effects of lead on intelligence has been determined to be 10 µg/dL

* Adapted from CDC, 1992. (Environ. Health Perspect. 1996; **104**: 146 - 7)

a Safe blood lead levels have <u>not</u> been determined for foetuses or children

b Both biological and toxicological effects may occur at levels as low as 6 - 7 µg/dL; Schwartz finds a
 continuum of lead effects down to 1 µg/dL. <u>No absolute threshold level has been identified</u>.

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GENERAL LITERATURE REVIEW [#]

The health effects of lead exposure have been noted for many years and have been extensively reviewed (WHO 1995; Bascom et al 1996; Needleman and Bellinger 1991). The route of exposure to lead is through both inhalation and ingestion. About 20 to 60% of inhaled lead particles at the size range found in the atmosphere are deposited in the human respiratory tract (Schlensinger 1988). The amount of deposition varies with particle size, rate and depth of respiration, and the age and sex of the individual which determines the size of the airways. Most of the deposited lead is cleared through mucocilliary clearance of particles deposited on conductive airways, phagocytosis by alveolar macrophages, a and the absorption into the systemic circulation (Morrow et al 1980). Lead containing macrophages may also migrate to the airways and be cleared by the muco-ciliary blanket and swallowed. Approximately 10% is absorbed in the gastrointestinal tract by adults and considerably more than that by children.

Foetuses, infants and children are considered to be more susceptible to the adverse effects of lead exposure because of smaller body size, incompletely developed nervous systems, higher rates of gastrointestinal absorption and rapid growth. Animal and epidemiologic studies have shown that low-level exposures have adverse effects on the development and function of the central nervous system. These effects have been extensively reviewed (WHO 1995; Cory-Slechta 1995a,1995b; Winneke 1995; Laughlin 1995; Rosen 1994; Bellinger and Stiles 1993; Preuss 1993; Otto and Fox 1993; Bressler 1991; Needleman and Bellinger 1991). The effect of blood lead on IQ is estimated to be between 1 and 3 points per 10 μg/dL increment in blood lead as assessed at 4yrs and above. At blood lead levels greater than 25 μg/dL this relationship may differ. Existing epidemiological studies do not provide definitive evidence of a threshold for these effects (WHO 1995).

Because of retention of lead in bone, conditions associated with increased bone catabolism may lead to increased circulating blood lead concentration even when environmental exposures have been reduced or eliminated. Thus women with previous lead exposures may have elevated blood lead levels during pregnancy, and their unborn children may be exposed transplacentally, and newborns through breast milk (Bascom et al 1996; Andrews et al 1994). Similarly, diseases that produce excess bone turnover may be associated with further elevation of blood lead levels (eg., hyperthyroidism and osteoporosis). The adverse effect of lead on pregnancy outcomes has been well documented for high lead doses and include sterility, spontaneous abortion and stillbirth. The effect of low level lead exposure on pregnancy outcomes has been reviewed by O'Halloran and Spickett (1992/1993). Preterm delivery, congenital abnormalities, growth stature and birth weight have all been identified as being affected by maternal blood lead levels.

[#] Literature review undertaken by Dr. Lyn Denison, PhD., EPA Victoria.

Several recent investigations suggest an association between high blood pressure and elevated blood lead levels (Schwartz 1995; Staessen et al 1994; Nowack et al 1992). Lead exposure has also been suggested as being associated with chronic renal disease (Nuyts et al 1991) and nephrotoxicity (Nolan et al 1992).

The genotoxicity of lead has been reviewed by Winder and Bonin (1993). The results of several studies as reviewed by Winder and Bonin show varying results which may in part be due to the low solubility of lead compounds in biological fluids, chemical interferences, nonspecificity of the assays used, the delivery of toxic doses to specific genetic processes or the mediation of genotoxicity through indirect mechanisms. In a review by Hartwig (1994) lead (II) compounds were noted to be mutagenic after long incubation times and induced DNA strand breaks only after treatment with high, toxic doses. Indirect genotoxic effects were noted after at low, non-toxic concentrations suggesting an interference with DNA repair processes.

This current document reviews recent literature on the adverse health effects of exposure to lead. In the absence of industrial sources, lead exposure from ambient air is considered to be a minor source. Relating blood lead levels to exposure from airborne lead is difficult. WHO (1995) has quoted that a $1\mu g/m^3$ increase in air lead gives rise to a 1 $\mu g/dL$ increase in blood lead. They consider that this is the best estimate for the blood lead/air lead relationship in a non-occupational setting.

Epidemiology

In a recent study by McDonald and Potter (1996), the effects of lead poisoning in children has been assessed in terms of early and late mortality. In this study 454 paediatric hospital patients who were diagnosed with lead poisoning between 1923 and 1966 were traced through to 1991 to examine possible mortality effects. Of the 86 deaths observed, 17 were attributed to lead poisoning. Mortality from all causes was about 70% higher than expected in both males and females and excess deaths were observed to be associated with several organ systems. Mortality from cardiovascular causes was elevated with an observed/expected (O/E) mortality ratio of 2.1 and cerebrovascular deaths were particularly common among women (O/E = 5.5).

Other diseases for which elevated O/E mortality ratios were observed were pancreatic cancer (O/E = 10.2) and non-Hodgkin's lymphoma (O/E = 13.0). Mental retardation ranging from mild to profound was also found in the study population. Blood lead levels at the time of poisoning were not known as tests were not conducted prior to 1963 at this hospital. However, the presence of symptoms such as encephalopathy or convulsion, consistent with a blood lead level of at least 70 $\mu g/dL$ was noted in 160 (35%) of the patients. Blood lead

tests performed post 1963 on 23 of the children revealed an average blood lead level of 113 µg/dL.

A weak but significant positive association between childhood dentine lead levels and BMI in both cross-sectional and longitudinal analyses of a group of Massachusetts school children (Kim et al 1995). A 10-fold increase in dentine lead level was associated with an increase of 1.02 kg/m² in BMI at the age of 7 years. A 10-fold increase in dentine lead level was also associated with an increase in BMI of 2.65 kg/m² from age 7 to 20 yrs. This study showed that bone lead levels at the age of 20 yrs were not significantly associated with any growth changes between 7 and 20 yrs. Average dentine lead levels were 14.9 ppm over the study period 1975 to 1978, and 12.9 ppm for the period 1989 to 1990.

Blood lead levels have been found to be negatively correlated with stature. To examine this relationship further, Huseman et al (1992) looked at the possible neuro-endocrine effects of lead in children. Two groups of children with different lead exposures were studied during and after chelation therapy. All children studied showed growth retardation during toxic blood lead. Mean peak human growth hormone responses to provocative stimuli were lower during blood lead, but the responses were all within normal limits. Insulin-like growth factor I values showed an inverse correlation with toxic blood lead up to 40 µg/dL Basal thyroid-stimulating hormone, prolactin, thyroxine, and tri-iodothyronine concentrations were not affected by blood lead. In addition, thyroid stimulating hormone and prolactin responses to thyrotropin releasing hormone were not affected by toxic or low blood lead. The authors concluded that these observations indicate that lead-induced short stature may be due to diminished human growth hormone secretion, which in turn results in reduced insulin-like growth factor I secretion, or that lead may also directly inhibit insulin-like growth factor I formation.

As part of the Normative Ageing study, the association between renal function and blood lead levels was investigated in a group of men aged 43 to 90 yrs recruited from the Boston area irrespective of previous lead exposure (Payton et al 1994). Decreased creatinine clearance was found to be significantly associated with increased blood lead. A rise in blood lead of 10.0 µg/dL was associated with a decrease in the log creatinine clearance rate of 10.4 ml/minute. This relationship persisted after adjustment for age body mass index. The mean blood lead concentration and creatinine clearance rates were 8.1 µg/dL and 88.2 ml/minute respectively.

In a meta analysis by Schwartz (1995) a strong significant association has been found between lead exposure and increases in systolic blood pressure in men. A decrease of blood lead from 10 µg/dL to 5 µg/dL has found to be associated with a decrease of 1.25 mmHg in systolic blood pressure. The association was robust to deletion of the most significant study or the addition of 8 studies showing no effect. An earlier study by Schwartz found that an association

existed between blood pressure and blood lead in both men and women aged between 20 and 74 yrs after controlling for age, race and body mass index (Schwartz 1991). The association was weaker for women than for men. Blood lead was also a significant predictor of left ventricular hypertrophy.

In an earlier meta analysis, Staessen et al (1994) found that the association between blood pressure and blood lead was similar in both men and women. A two-fold increase in blood lead concentration was associated with a 1 mmHg increase in systolic pressure and a 0.6 mmHg increase in diastolic pressure. No dose response relationship between mean blood levels and association was observed across the studies. Blood lead levels in these studies ranged from 0.31 to 2.18 µmol/L.

Blood lead has also been associated with increases in blood pressure in men aged 55 to 75 yrs in a study from Rome (Menditto et al 1994). Median blood lead levels increased significantly from 111 µg/L in subjects with normal blood pressure to 113.5 µg/L in subjects with borderline high blood pressure and to 120 µg/L in subjects with increased blood pressure. After controlling for body mass index, age, heart rate, skinfold thickness, serum lipids and glucose levels, blood lead was still a significant predictor of increased systolic and diastolic blood pressure. The regression coefficient was 5.6 mmHg/ln(µg/L) for systolic blood pressure and 1.7 mmHg/ln(µg/L) for diastolic blood pressure. After controlling fro alcohol consumption, the association between blood lead and increased blood pressure was only observed in drinkers. The median blood lead concentration in the study sample was 113 µg/L with a range between 40 and 442 µg/L.

In a study from Denmark, blood lead was found to be associated with blood pressure and total mortality (Møller and Kristensen 1992). During the study period (1976 to 1987), the mean blood lead level fell by approximately 30% in both men and women. Blood lead levels ranged from 2 to 62 µg/dL with mean levels ranging from 13.6 µg/dL in 1976 to 8.3 µg/dL in 1987 in men, and 9.6 µg/dL in 1976 to 6.8 µg/dL in 1981 for women. An increase in blood lead level of 4 µg/dL was found to correspond to an increase in systolic blood pressure of 1 mmHg. No significant association was found for diastolic blood pressure and blood lead. Blood lead was also a significant predictor of total mortality, but the association was weaker when alcohol intake was accounted for.

A study designed to evaluate the early health effects of occupational exposure to lead compared health impacts in 3 cohorts: (1) gasoline depot workers; (2) traffic police; and (3) controls (office workers). Mean external lead exposure concentrations were 84.8 µg/m³ for the depot workers, 5.4 µg/m³ for the traffic police and 1.1 µg/m³ for the controls. No significant subclinical indications of lead toxicity were found between the control group and the traffic police. This may in part be due to the small sample size of traffic police in this study. However, in the depot workers there was a significant increase in the frequency of the appearance of tremor and sinus bradycardia compared to the controls.

Small differences were noted in total lead levels in urine within groups before and after work. Both the depot workers and traffic police had significantly higher lead levels in the urine compared with the control group. No blood lead levels were available for this study.

An analysis of the epidemiologic literature by Andrews et al (1993) has shown that prenatal lead exposure is unlikely to increase the risk of premature membrane rupture but does appear to increase the risk of preterm delivery. Prenatal lead exposure was also found to be associated with reduced birth weight, but the resulted were found to be dependent on study design and the degree of control for confounding.

Conclusions

The adverse health effects of lead exposure are varied. Recent studies have indicated that these effects are observed at blood lead levels lower than those previously considered with particular regard to impairment of neural development, intellectual capacity, leading to behavioural and learning difficulties.

prenatal lead exposure appears to be associated with preterm delivery and reduced birthweight, however current epidemiological data would seem to be affected by confounding factors, and further studies are required.

The effects of lead exposure during childhood have been shown to continue into later life with mortality effects in adult life attributed to childhood lead poisoning. Lead exposure has also been associated with increased body mass index and short stature. This may be due in part to diminished human growth hormone secretion, which in turn results in reduced insulin-like growth factor I secretion. It is also possible that lead may also directly inhibit insulin-like growth factor I secretion.

Associations between blood pressure and blood lead levels have been observed. These effects have been observed in both men and women, and may result in the longer term in increased mortality from stroke and myocardial infarction. There is some evidence that these effects may be explained at least in part by the effects of lead on renal function leading on to nephrotoxicity and renal insufficiency.

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A Review on Existing Health Data on Six Pollutants
Prepared by Dr Jonathon Streeton for the National Environment Protection Council

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APPENDIX 3 -
HEALTH EFFECTS OF NITROGEN DIOXIDE

SUMMARY

An assessment of the adverse health effects of nitrogen dioxide (NO_2) presents a somewhat conflicting pattern of disturbances in respiratory function, increase in lower respiratory tract symptoms in children, aggravation of asthma, impairment of lung defences, and more recently, a suggestion of an effect on daily mortality, particularly in older compromised adults. It is quite probable however that the conflicting epidemiological data reflects the known interactions between NO_2 and other pollutants, in particular, fine respirable particles ($PM_{2.5}$) and ozone (with which NO_2 bears an inverse relationship).

Statistical reviews of the available epidemiological and controlled exposure data, based on predominantly short term ambient exposures, would suggest that the current lowest observed adverse effect level (LOAEL) is in the range of 0.2 - 0.3 ppm, however there is an increasing body of data to suggest that longer term chronic indoor exposure to significantly lower concentrations of NO_2, of the order of 0.04 - 0.08 ppm during early and middle childhood years can lead to the development of recurrent upper and lower respiratory tract symptoms, such as recurrent 'colds', a productive cough and an increased incidence of respiratory infection with resultant absenteeism from school.

A safety factor needs to applied to any LOEL in order to ensure adequate protection of the more vulnerable sub-groups in the population - the young, asthmatics of all ages but especially children, and compromised adults with chronic respiratory and cardiac disorders. Currently, this safety factor is generally regarded as being of the order of 50% of the LOEL, which would suggest that standards / guidelines should be in the range: 0.10 - 0.15 ppm for shorter term exposures (1 hour averaging period), and in the range: 0.02 - 0.04 ppm for longer term exposures (annual averaging period) to ensure there is adequate protection for the more susceptible individuals in the community.

GENERAL COMMENT [#]

The health effects of NO_2 have been extensively reviewed by a number of jurisdictions over the last several years (Bascom et al 1996; DoE 1996;WHO 1995; WHO 1994; Concawe 1995; US EPA 1995; US EPA 1993; DoH 1993; Berglund et al 1993). In addition, reviews of the health effects of NO_2, with a view to readjustment of current recommended guidelines, have been in progress in some other jurisdictions such as the current WHO/EURO revisions of *"Air Quality Guidelines for Europe"* (Maynard 1996; 1997), however at the time of preparation of this review, formal permission for public release is not available). Other current reviews, as yet unpublished, include the WHO/IPCS review of the 1977 WHO Environmental Health Criteria (No.4) *"Oxides of Nitrogen"*, and a review by the UK Department of the Environment (DoE) Expert Panel on Air Quality Standards. There is therefore available a wide literature on the epidemiology and the toxicology of the adverse health effects of NO_2 upon both humans and experimental animals.

Notwithstanding the range of literature available, the health impacts of NO_2 on exposed human populations remain equivocal. Nitrogen dioxide appears to contribute both to morbidity and to mortality, especially those susceptible subgroups such as young children, asthmatics, and in those individuals with chronic inflammatory airway disease (chronic bronchitis and related conditions). Nitrogen dioxide appears to exert its effect on the human organism both directly leading to an inflammatory reaction on epithelial surfaces in the human lung due to an oxidative reaction on unsaturated fatty acids in cell membranes and in various soluble and structural proteins, resulting in the production of inflammatory mediators; and indirectly by the induction of relative impairment of immune defence mechanisms in the lung. Epidemiological studies would suggest that young children are especially susceptible to these effects, resulting in potentiation of respiratory infections following disturbances in immune defence mechanisms.

Nitrogen dioxide has also been demonstrated to potentiate the effects of exposure to other known irritants such as ozone (Hazucha et al 1994), sulfur dioxide (Devalia et al 1994) and respirable particles (DoH 1993). Although outside this specific review, attention must be drawn to the increasing literature now available on the impact of mixtures of air pollutants on the human population. A recently published review from London (DoH 1995) is a useful reference source at this time, although it is clear that very considerable investigative work has yet to be done to more specifically define the health impacts which might result from exposure to these pollutant mixtures. Indeed, it may well be demonstrated in the future that many of the currently observed discrepancies in the effects of NO_2 are in fact due to inflammatory responses secondary to exposure to by-products of NO_2, namely nitrates, in the form of

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fine respirable particles ($PM_{2.5}$). Conversely it is possible that in higher concentrations, the presence of nitrites may act as bronchodilators, resulting in inverse dose-response relationships (DoH 1993).

The community observed health effects of NO_2 exposure have been especially noted in recent studies in the indoor situation primarily due to the presence of unflued or poorly vented gas fired appliances (a recent example is the study by Jarvis et al 1996, with an accompanying editorial comment by Brauer and Kennedy 1996). The study undertaken by Neas et al 1991 as part of the Havard Six Cities Study shows particularly convincing evidence for the association between indoor NO_2 exposures and an increased incidence in lower respiratory symptoms. Pilotto observed a significant increase in lower respiratory tract symptoms in NSW children living in gas- appliance homes and/or attending gas-heated schools. Neas et al noted that in a large group of children (nearly 1600 aged 7 - 11years), a 15 ppb increase in the mean annual household NO_2 levels was associated with a cumulative increase in the incidence of lower respiratory tract infections.

Studies undertaken worldwide have repeatedly shown robust epidemiological associations between chronic NO_2 exposure, measured either directly, or by inference due to the associated presence of unflued gas stoves and gas heaters, and the incidence of coughing, wheezing, and respiratory infections in exposed children - especially those of a young age. Indoor exposures to NO_2 have, in many studies, been shown to greatly exceed the comparable measured outdoor or ambient exposures to the same population, and frequently for much extended periods. Animal studies have demonstrated that extended exposure over several months have been required to demonstrate changes in lung structure, lung metabolism, and lung defences against bacterial and viral infections.

In the Australian context, there have been several epidemiological studies undertaken in various states which, to varying degrees, all demonstrate community response patterns consistent with current overseas experience. These studies will be discussed in more detail subsequently, but mention is made at this point of results from the recent HARP project undertaken in Sydney. Morgan et al 1996a (personal communication) in their review of the relationships between hospital admissions for respiratory and cardiac conditions and observed air pollution patterns in the Sydney metropolitan region for the years 1990 - 1994, with adjustment for seasonal and cyclic factors, that an increase in NO_2 levels from the 10th to the 90th centile resulted in a 7.23% increase (95%CI: 1.97 - 12.76) in hospital admissions for childhood asthma, and a 7.2% increase (95% CI: 4.25 - 10.24) in admissions for heart disease. Morgan et al also found that when multiple pollutant models were examined, increases in NO_2 were found to be primarily responsible for the increases in admissions for childhood asthma and for heart disease in the elderly, whereas increases in particulates were found to be largely responsible for the observed increases in admissions for exacerbations of chronic airways disease.

In a separate series of analyses, which examined air pollution effects on mortality in the Sydney metropolitan region, for the years 1989 - 1993, with adjustments for seasonal and cyclic factors, Morgan et al 1996b (personal communication) found that an increase in NO_2 levels from the 10th to the 90th centile resulted in an increase of 7.71% (95% CI: -0.34 - 16.40) for mortality from respiratory causes, and that multiple pollutant models suggested that effects from NO_2 were on respiratory mortality, whereas particulates and ozone had effects on 'all cause' mortality and on cardiovascular mortality. Furthermore, it was noted that these observed mortality effects were independent of the effects of other pollutants.

There would appear to be separate patterns of responses in susceptible populations to short term acute ambient exposures, in comparison to the responses observed after longer term chronic exposures to mildly increased background concentrations in the indoor environment. With acute ambient exposures, generally to a mixture of pollutants including NO_2, photochemical oxidant (ozone), and respirable particles, immediate effects within one to two days can be demonstrated in the form of increased bronchial hyper-responsiveness in asthmatics; and in those with chronic inflammatory lung disease, leading to increased frequency of wheezing, cough, sputum production, with, as a secondary effect, increased frequency of respiratory infections (DoH 1995). On the other hand, longer term exposure in a chronic indoor environment appears to have more direct effects on the patterns of respiratory infection in young children presumably due to disturbances in pulmonary airway immune defence mechanisms.

Whereas exposures of healthy non-asthmatic young adolescents to increased ozone containing environments have been shown to lead to increased airways responsiveness resulting in statistically significant falls in lung function particularly whilst exercising, this response pattern has not been demonstrated with NO_2. Rather the effects of NO_2 in the younger human population appeared to be limited to children from infancy through to late childhood , but with the major effects being demonstrated in children ages 5 to 12 who have been estimated in having as much as a 20% increased risk for respiratory symptoms and disease for each increase of 0.015 ppm of NO_2 where the weekly average concentrations for NO_2 are in the approximate range of 0.08 to 0.065 ppm, or possibly higher (WHO 1994). For practical purposes however, it has not been possible in the majority of epidemiological studies to satisfactorily separate the effects of indoor and outdoor (ambient) exposures.

At present, the meta-analysis undertaken by Folinsbee (1992) remains the most reliable basis for determining a LOAEL for NO_2, at between 0.20 and 0.30 ppm (200 - 300 parts per billion) exposure over one hour. Current review by the WHO and the European Union (R. Maynard, personal communication), and also by Concawe (Concawe 1995,1996a, 1996b) would

confirm this LOAEL, on the basis of demonstrating reversible changes in respiratory function of a greater than 5% reduction in FEV1.0, and also increased airway responsiveness in mild asthmatics following 30 minutes exposures, on top of which a 50% safety margin is proposed, reducing the current WHO/EURO guideline to 0.11ppm mean over 1 hour. It should however be noted that as an alternative to establishing a short term objective, another option is to consider a longer term (annual) objective as has been the recently re-confirmed NAAQS for the United States (USEPA 1995), which remains 0.053 ppm annual arithmetic average (which in turn approximates to a one hour objective of 0.20 ppm).

It should be noted that epidemiological studies when subjected to meta-analysis do indicate that in children exposed to long term background increases in NO_2 of the order of 15 ppb demonstrate an increase in risk of illness odds of approximately 20%. This effect is not seen in adults with similar exposures. Further work will be necessary to more specifically identify the response patterns in identified risk subgroups.

There does not appear to be a simple linear relationship between NO_2 exposure and adverse health outcomes. It is difficult to summarise the inconsistent results of many epidemiological and experimental studies which have characterised exposure in different ways and examined different outcomes. There are no clear threshold levels for most health effects. Indeed some of the data may be better described by a U shaped relationship (Harrington & Krupnick 1995), which suggests that guidelines should recommend a 'safe range' rather than a single level.

Some epidemiological studies have found significant effects of NO_2 upon mortality, hospital admissions, emergency room visits and respiratory illness. The magnitudes for the relative risk of death are weak ranging from 1.0 (no effect) to 1.9 for mean NO_2 levels between 35 and 88 µg/m3. The risk of hospital treatment appears to be increased only 1.1 to 1.3 fold by levels ranging from 38 to 528 µg/m3. The risk of respiratory illness appears to increase by only 1.2 to 1.8 fold for NO_2 levels between 0.0083 ppm and 502 µg/m3. The effects upon lung function are modest with only a 40 litres/minute reduction in peak expiratory flow rates for every 20 µg/m3 increase in NO_2, and a 5% reduction in FEV1.0 / FVC for every 10 µg/m3 increase in NO_2 above 40 µg/m3. In themselves, these results do not provide a firm scientific basis for setting health based exposure guidelines.

The experimental (controlled exposure) studies have been able to control for many of the confounders which affect the epidemiological studies. However they still yield inconsistent findings, even in subjects such as young asthmatics who would be expected to be most sensitive to the effects of NO_2. There are some studies suggesting a reduction in lung function in patients with chronic obstructive pulmonary disease (COPD) and potentiation of exercise-induced asthma following exposure to 0.3 ppm NO_2. One study found evidence of increased airway inflammation in asthmatics exposed to 1.0 ppm NO_2. Higher

levels (5 - 8 ppm) appear necessary to increase airways resistance in normal subjects. Yet paradoxically, some studies which have exposed subjects with COPD to 2.0 ppm have not found any adverse effects. As noted above however, Folinsbee in his meta-analysis (Folinsbee 1992) was of the opinion that 0.2 - 0.3 ppm NO_2 over one hour resulted in a statistically significant increase in bronchial hyper-reactivity.

Some of the inconsistent findings may be due to interactions between NO_2 and other pollutants, allergens and viruses (DoH 1993, DoH 1995). There is a well described chemical reaction between ozone and NO_2 which explains inverse relationships between the two pollutants in ambient air and the resulting adverse health effects. Allergen challenge experiments clearly show that pre-exposure to 0.4 ppm NO_2 increases both the early and the late asthmatic reactions to house dust mite (Tunnicliffe et al 1994). The weight of evidence now available suggests that NO_2 can impair respiratory defences to viral infection. Although infection with attenuated influenza virus was not significantly promoted by exposures to 1.0 -3.0 ppm NO_2 (Goings et al 1989), these experiments have been considered to have only limited statistical power (Samet & Utell 1990).

Further epidemiological studies are needed to characterise exposure to other pollutants and allergens as fully as possible using standardised methods. These further experimental studies should investigate, amongst other things, the combined effects of NO_2 and other pollutants upon a wider range of subjects using state of the art techniques such as bronchoscopy, cell analysis, mediator profiles, etc. Only when this information is available may it be possible to more accurately define the dose response relationships for NO_2, especially with regard to the effects of low background levels of chronic exposure, either outdoors or indoors. Epidemiological and controlled exposure data are summarised in Table 1 of this Appendix.

In conclusion, the currently recognised adverse health effects following exposure of human populations to low levels of NO_2 remain equivocal, with conflicting patterns of results being obtained in both controlled exposure studies and in community epidemiological studies. The contribution of NO_2 as one of a mixture of pollutants in the ambient environment has yet to be clearly defined.

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LITERATURE REVIEW [#]

Introduction

Nitrogen dioxide has been shown to produce lung cell injury and/or death and other respiratory effects in humans and animals exposed both acutely and chronically. The principle mechanisms of toxicity associated with NO_2 inhalation involves oxidation of unsaturated fatty acids in cell membranes and of functional groups in soluble and structural proteins (Moldeus, 1993; Sandstrom, 1995; Bascom et al., 1996; Menzel, 1994). Support for this type of mechanism of toxicity is provided by studies which have shown an increase in both lipid peroxidation products and in lung antioxidant enzymes immediately following exposure to NO_2. The fundamental mechanism of pulmonary oedema resulting from exposure to NO_2 may be due to cytotoxic effects of NO_2 directly on epithelial cell membranes, while the mechanism responsible for increased susceptibility to viral and bacterial infection may be the cytotoxicity of NO_2 on membranes of alveolar macrophages. The above mechanisms of toxicity are generally considered to be related to those health effects of NO_2 which are of greatest public health concern.

Epidemiology

The epidemiological evidence on NO_2 exposure covers a wide range of health effects, from acute annoying upper and lower respiratory tract reactions and disturbances in lung function to chronic pulmonary disorders, such as asthma and chronic bronchitis. More recent studies have also shown a correlation between daily mortality and NO_2 levels.

Mortality

Hourly NO_2 and O_3 levels were associated with mortality in the elderly and with cardiovascular mortality during the summer months in Barcelona for the period 1985-1991 (Sunyer et al., 1996). The mean hourly level of NO_2 during the study period was 88 $\mu g/m^3$ with a maximum of 339 $\mu g/m^3$. Relative risks per 100 $\mu g/m^3$ increase in NO_2 of 1.05 and 1.07 were observed for elderly mortality and cardiovascular mortality respectively.

Kinney and Ozkaynak (1991) found significant associations between NO_2 and daily mortality from all non accidental causes, and cardiovascular deaths. Daily NO_2 levels were highly correlated with CO and particulate levels making it impossible to conclusively separate the individual effects. The mean NO_2 level for the entire study period (1970 to 1979) was 69 ppb.

An ecological study of infant mortality and air pollution was conducted in the Czech Republic for the period 1986-1988 (Bobak and Leon, 1992). A weak positive association was observed between post neonatal mortality and daily NO_2 levels. The risk ratio from the lowest to the highest quintile of NO_2 for post neonatal respiratory mortality was 1.9. The mean NO_2 level during the study period was 35.1 $\mu g/m^3$.

Weak positive associations between NO_2 and daily mortality were found in a study from London for the period 1987-1992 (Anderson et al, 1996). The mean 24 hour average NO_2 level for the study period was 37.2 $\mu g/m^3$ with a maximum of 182 $\mu g/m^3$. The mean maximum 1 hour level was 57.2 $\mu g/m^3$ with a maximum of 370 $\mu g/m^3$. Associations were found for all cause mortality (1 day lag) and cardiovascular mortality (1 day lag) with 1 hour maximum NO_2. A negative effect was seen for respiratory mortality (2 day lag). All associations were observed during the warm months. The association for all cause mortality became insignificant when O_3 or SO_2 were included in the model but was unaffected when black smoke was included.

A significant association between daily mortality for respiratory causes in children under 5 years of age and NO_2 levels in Sao Paulo, Brazil, was observed for the period 1990-1991 (Saldiva et al, 1994). The mean level of NO_2 during the study period was 0.127 ppm. Considering the mean levels of NO_2 in Sao Paulo, the odds of dying due to respiratory causes was estimated to be 1.3. Deaths due to non-respiratory causes were not associated with NO_2 levels. No other pollutant showed any association with mortality in this age group.

A study conducted in Lyon, France between 1985 and 1990 showed no association between daily mortality and NO_2 levels (Zmirou et al., 1996). The average NO_2 level during the study period was 70 $\mu g/m^3$ with a maximum value of 324 $\mu g/m^3$. There was also no association observed between daily mortality and O_3 but strong significant associations were found for SO_2 and $PM_{13.}$

An analysis recently undertaken in Sydney as part of the HARP project (undertaken jointly by the NSW EPA and the NSW Health Department to examine the determinants and characteristics of air pollution in the Sydney basin and the possible effects that pollution might have on human health) has shown evidence of a significant impact on mortality patterns as a result of ambient NO_2 exposure. Morgan et al 1996a (personal communication) undertook a times-series analysis of counts of daily mortality and major outdoor pollutants (ozone, particulates, NO_2) in Sydney for the years 1989 - 1993, with adjustments for seasonal and cyclical factors. An increase in NO_2 levels from 10th to the 90th centile was found to result in a 7.71% (95%CI: -0.34 - 16.40) increase in mortality from respiratory causes, and that when multiple pollutant models were examined, the effects of NO_2 were independent of the effects of the other pollutants assessed. In comparison, similar increments in particulates (measured as light scattering by integrating nephalometry and subsequently expressed as PM_{10}) resulted in a 2.63% (95%CI: 0.87 - 4.41) increase

in 'all cause' mortality and a 2.68% (95%CI: 0.25 - 5.16) increase in cardiovascular mortality; and for ozone, a 2.04% (95%CI: 0.37 - 3.73) increase in 'all cause' mortality and a 2.52% (95%CI: -0.25 - 5.38) increase in cardiovascular mortality.

Another recent local Australian mortality study was undertaken by Simpson et at 1995a, who reviewed possible associations between daily mortality and air pollution in Brisbane. This study examined daily mortality patterns for the years 1987 - 1993, in an area which has generally low levels of atmospheric pollution in comparison to other reported areas elsewhere in Australia. Together with particles(PM_{10}), SO_2, and ozone, NO_2 was also assessed. The study found that notwithstanding the low levels of pollutants in the Brisbane region, the mortality relationships described elsewhere appear to hold for Brisbane also, especially for PM_{10}, but also quite strongly for ozone, and, to a weaker extent, also for NO_2 although the impact of weather and related variables has a significant confounding effect.

Hospital Admissions and Emergency Room Visits

Hospital admissions for respiratory disease in two cities in the Netherlands, Amsterdam and Rotterdam, showed mixed results with respect to an association with NO_2 levels (Schouten et al, 1996). No clear effect of NO_2 was observed for Amsterdam, however a non-significant positive effect was observed in Rotterdam. Admissions for respiratory disease, COPD and asthma were investigated. The mean 24 hour NO_2 level during the study period was 54 $\mu g/m^3$ and mean maximum 1 hour level was 82 $\mu g/m^3$.

Strong associations were observed between the 24 hour mean level of NO_2 and hospital admissions for asthma in Paris for the period 1987-1992 (Dab et al, 1996). The relative risk per 100 $\mu g/m^3$ was found to be 1.175 (no lag). Associations were also found for 1 hour peak NO_2 levels. The mean 24 hour NO_2 level during the study period was 45 $\mu g/m^3$ with a 99th percentile value of 108.3 $\mu g/m^3$. The mean 1 hour daily maxima NO_2 level was 73.8 $\mu g/m^3$ with a 99th percentile value of 202.7 $\mu g/m^3$.

The short-term effects of air pollution on hospital admissions for respiratory and cardiac causes has been investigated in Athens during 1988 (Pantazopoulou et al, 1995). Significant associations were observed for both cardiac and respiratory admissions and maximum daily 1 hour levels for NO_2, black smoke and CO during the winter months but not the summer. The average increase in the number of cardiac admissions corresponding to an increase from the 5th to the 95th percentile of NO_2, ie., 76 $\mu g/m^3$, was approximately 11% or 1.4% per 10 $\mu g/m^3$. For respiratory admissions a 1% increase per 10 $\mu g/m^3$ in NO_2 was observed. The mean NO_2 level during the winter months was 94 $\mu g/m^3$ and during the summer 111 $\mu g/m^3$.

Hospital admissions and emergency room visits for asthma have been found to be highly significantly correlated with NO_2, SO_2, NO, CO and TSP in Helsinki (Ponka et al., 1991). The effect of gaseous pollutants was greater than that of TSP. During periods of high pollution the mean number of hospital admissions attributed to NO_2 pollution was 29% higher compared to periods of low pollution. The mean monthly NO_x concentrations in the more polluted area ranged between 8 and 33 µg/m³ with maximum half-hour concentrations ranging 38-528 µg/m³.

Emergency room visits for asthma in Barcelona were found to be associated with daily NO_2 levels for the period 1985-1989 (Castellsague et al., 1995). This association was observed in both summer and winter with the strongest association in summer found for the current and previous 5 days NO_2 level with a 7.1% increase per 25 µg/m³ in NO_2. The increase in emergency room visits per 25 µg/m³ NO_2 was 4.5% in summer and 5.6% in winter. In winter the mean of the current and previous 2 days NO_2 levels was associated with a 7.2% increase in emergency room visits. Mean NO_2 levels during the study period were 104 µg/m³ and 100.8 µg/m³ for the summer and winter respectively.

A study from Oulu, Finland has shown that emergency room visits for asthma were strongly associated with NO_2 levels for the period 1985 to 1986 (Rossi et al., 1993). The daily mean NO_2 level was 13.4 µg/m³ with a daily maxima of 15.4 µg/m³. Significant correlations were also found for SO_2 and TSP.

In the Australian context, there have been some recent studies. Abramson et al 1994 reviewed the relationships between air pollution, meteorological conditions, air-borne pollens and asthma admissions in the Melbourne metropolitan region. This study, available thus far only as an abstract, used spectral and state-space analysis to show that 23% of the daily variation in asthma admissions could be explained by the impact of specific environmental factors (13.2% by ozone, 1.0% by particles, but only 0.8% by NO_2). Further analyses have yet to be undertaken and reported.

A study by Morgan et al 1996b is of considerable local importance. This study, a companion to the mortality study by the same authors as already described, is an assessment of the impact of air pollution on hospital admissions in Sydney for the years 1990 - 1994. As with the mortality study, a time series analysis of counts of daily hospital admissions for asthma, chronic obstructive airways disease, and heart disease with major pollutants (ozone, NO_2, and particulates) in the Sydney metropolitan region, with adjustment for cyclical factors was undertaken. Morgan et al found that an increase in NO_2 levels from the 10th to the 90th centile resulted in a 7.23% (CI: 1.97 - 12.76) increase in hospital admissions for childhood asthma (ages 1 - 14 years), and also a 7.2% (CI: 4.25 - 10.24) increase in admissions for heart disease. When multiple pollutant models were assessed, it appeared that NO_2 is primarily responsible for the increases in admissions for both childhood asthma, and for heart disease in the elderly, whereas the increases in admissions for chronic obstructive airways disease

appear to be primarily due to particulates. Risk assessments were also undertaken looking at the dose response relationships between asthma and the daily maximum 1 hour NO_2 levels (ppb). Indeed, the relationship is linear, with an RR =1 for NO_2 of 15 ppb, increasing to an RR = 1.04 for NO_2 of 40 ppb. With heart disease, there is a steep increase from approx. 20 ppb (RR= 1) to 40 ppb (RR = 1.07).

Respiratory Illness

Numerous epidemiologic studies have attempted to demonstrate an association between NO_2 exposure and respiratory illness using a variety of health endpoints (for reviews see Bascom et al., 1996; Pershagen and A study from Oulu, Finland has shown that emergency room visits for asthma were strongly associated with NO_2 levels for the period 1985 to 1986 (Rossi et al., 1993). The daily mean NO_2 level was 13.4 $\mu g/m^3$ with a daily maxima of 15.4 $\mu g/m^3$. Significant correlations were also found for SO_2 and TSP (Norberg, 1993). Early studies by Shy et al., (1970b) tracked the respiratory symptoms of 871 families selected from 5 schools situated near a munitions factory in Chattanooga, Tennessee. An 18.8% increase in respiratory illness was found among families exposed to elevated levels of NO_2. The ambient 24-hour mean NO_2 level was 0.083 ppm in the high exposure area, 0.063 ppm in the intermediate area and 0.043 ppm in the low exposure area. No linear dose response relationship could be determined for the relationship between NO_2 levels and incidence of respiratory illness.

In a further study conducted in Chattanooga, Harrington and Krupnik (1985) found a statistically significant association between NO_2 levels and acute respiratory illness for children 12 yrs of age and younger. Again a linear dose response was not observed. More illness was found to be associated with low pollution values rather than high ones. Mean 24 hour NO_2 maximum values during this latter study were 98 $\mu g/m^3$.

The effects of long-term exposure to NO_2 with respect to chronic disease have been investigated in a cohort study of 6,000 non-smoking Seventh-day Adventists in California (Abbey et al., 1993). The disease outcomes considered included respiratory symptoms, cancer, myocardial infarction and natural all-cause mortality. Both ambient and personal monitoring was conducted with the aim of achieving the best estimate of actual personal exposure to NO_2 during the study period. The members of the cohort completed detailed questionnaires at various times between 1977 through to 1987. No statistically significant associations were found for mean concentrations of NO_2 and the development of new cases of respiratory symptoms or change in severity of respiratory symptoms. Also, no statistically significant associations were found between long-term ambient concentrations of NO_2 and incidence of cancer, myocardial infarction or all cause mortality.

Concern about adverse health effects of indoor exposure to NO_2 was first raised by reports from the UK and USA (reviewed in Bascom et al., 1996; Samet and Utell, 1990). These early reports suggested that the presence of a gas stove in a home increased the frequency of respiratory symptoms and of respiratory illness before 2 yrs of age. The methodological problems associated with assessing these data have been reviewed by Samet and Utell

(1990). In subsequent studies the association between respiratory symptoms and the presence of a gas stove has not been clear (Bascom et al., 1996).

A prospective cohort study by Samet et al (1993) found no association between nitrogen dioxide exposure and the incidence rates for any illness category (upper respiratory illness, lower respiratory illness, lower respiratory illness with wet cough, and lower respiratory illness with wheeze) in healthy children less than 18 months of age; nor was there any association between illness incidence and the presence of a gas stove. In addition there was no association between illness duration and exposure to NO_2 for the first 3 illness categories, however, at the highest nitrogen dioxide exposure category (> 40 ppb), there was a nonsignificant increase in the duration of the illness classified as lower respiratory illness with wheezing. In this study over 75% of measured NO_2 concentrations were less than 20 ppb. NO_2 levels in infants bedrooms in homes with gas stoves were 2 to 3 times higher than those with electric stoves.

Pilotto 1994 reviewed respiratory symptom diary cards for a cohort of school children in NSW living in gas-appliance homes or attending gas-heated schools, and compared their scores with those for children not in these conditions. The children were regarded as being exposed to NO_2 if the mean daily-timed NO_2 levels were above 0.04 ppm, and with spike levels of the order of 0.08 ppm or higher compared to background levels of 0.02 ppm or less in non-gas atmospheres. Pilotto observed that there was a significant increase in 'non-zero' symptom scores for colds and/or absenteeism, likewise for sore throats, cough with sputum, and lower respiratory tract infections involving cough and sputum. There was also a suggestion of an increased response effect with increasing spike levels of NO_2 exposure. Pilotto expressed the opinion that an NO_2 level of 0.04 ppm represented a level of concern, and suggested a maximum goal of 0.08 ppm should be considered with an averaging time of 6 - 8 hours.

Perhaps the most convincing estimate of the effect of indoor exposure upon respiratory symptoms in children was provided by Neas et al (1991). This study was undertaken as part of the Harvard Six Cities cohort study, which has been referred to elsewhere in the report. A cohort of 1567 white children aged between 7 and 11 years were examined over a 5 year period. Week long measurements of NO_2 were obtained at three indoor locations over 2 consecutive weeks in both winter and summer. Presence of major source such as a gas stove or kerosene heater led to an average 15 ppb increase in indoor NO_2 concentrations. This increase in NO_2 was associated with a 1.4 (95%CI 1.14 - 1.72) fold increase in the cumulative incidence of lower respiratory symptoms, which included shortness of breath, chronic wheeze, cough, phlegm and bronchitis. The risk estimate was adjusted for city, age, gender, socioeconomic status, family history and respirable particulates in the home, which meant the results were not confounded by these factors. Interestingly there was no significant effect of indoor NO_2 upon reported asthma or lung function.

Braun-Fahrlander et al (1992) showed that the incidence and duration of respiratory symptoms in 625 Swiss children between the ages of 0 to 5 yrs was associated with outdoor levels of NO_2 but not indoor. Yearly average levels of NO_2 in Swiss cities ranged from 60 to 140 $\mu g/m^3$. Symptoms and duration of respiratory illness were recorded in a daily diary for a 6 week period. The relative risk for the incidence of upper respiratory was 1.23 per 20 $\mu g/m^3$ for total NO_2 exposure. However, the relative risk associated with NO_2 indoors was highly insignificant with a value of 1.03 per 20 $\mu g/m^3$. The relative risk for the duration of respiratory illness associated with NO_2 outdoors was 1.13 for a 20 $\mu g/m^3$ increase. NO_2 levels indoors were not associated with the duration of any illness. NO_2 levels indoors ranged from 11 to 31 $\mu g/m^3$, while NO_2 levels outdoors were considerably higher ranging from 25 to 51 $\mu g/m^3$.

In a study from East Germany (Von Mutius et al., 1995) NO_2 levels were found to be associated with the increased risk of developing upper respiratory symptoms in children aged between 9 and 11 yrs. The odds ratio associated with NO_2 levels during the winter was 1.53 while for the summer was 1.82. NO_2 maximum levels during the high pollution periods ranged from 49 to 502 $\mu g/m^3$ and during the low period 89 to 261 $\mu g/m^3$. The low pollution period was between April and July, 1992 and the high period between October 1991 and March 1992.

Air pollution levels have been associated with rates of chronic cough, bronchitis and chest illness in children (Dockery et al, 1989). This study, conducted as part of the Six Cities Study, found weak positive associations between chronic cough and chest illness and daily NO_2 levels. Persistent wheeze and asthma were negatively associated with NO_2 levels. Yearly average NO_2 levels ranged from 6.5 $\mu g/m^3$ in Portage to 22.6 $\mu g/m^3$ in St. Louis and Steubenville.

A study conducted in NSW to investigate the effect of emissions from power stations on asthma found no correlation between NO_2 levels and the prevalence of asthma in children (Henry et al., 1991). NO_2 levels in the vicinity of the power station (Lake Munmorah) were considerably higher than those in the control area (Nelson Bay) with yearly average levels of 2.0 $\mu g/m^3$ and 0.3 $\mu g/m^3$ at Lake Munmorah and Nelson Bay respectively. Maximum hourly averages were 169 $\mu g/m^3$ and 75 $\mu g/m^3$ at Lake Munmorah and Nelson Bay respectively.

Brief mention will be made of a recent study by Simpson et al 1995b, who assessed the relationship between outdoor air-borne bioaerosols and the incidence of asthma in Brisbane. Data was collected during 1994 - 1995, using symptom diary cards, hospital attendance dates, indoor allergen levels, smoking, gas appliances, etc., and a search was made for "coherence". In short, minimal, if any, effect was shown relating air pollution factors to asthma

incidence, except for particles in various forms, and possibly a slight but weak effect from gaseous pollutants during the 1994 autumn.

Lung Function

In an early study conducted in Chattanooga, $FEV_{0.75}$ was found to associated with NO_2 levels in ambient air (Shy et al, 1970a). Lung function was found to be significantly lower in areas of high NO_2 pollution compared with control areas. Though significant these differences were small in magnitude. The data from this study suggest that lung function is adversely affected when a NO_2 threshold was reached, but above this threshold level no further impairment could be detected. Mean NO_2 levels ranged between 0.062 and 0.109 ppm in the high pollution area with 90th percentile values ranging from 0.098 to 0.242 ppm.

NO_2 levels have been associated with decreases in lung function in children as part of the NHANES II study (Schwartz, 1989). The decreases in FEV_1, FVC and PEF were found to occur at levels below 0.05 ppm.

In an 8-month prospective study from Denmark (Moseholm et al., 1993) increased levels of both NO_2 and SO_2 corresponded to decreases in peak flow in 27 asthmatic patients. In addition NO_2 and SO_2, at levels greater than 40 $\mu g/m^3$, acted synergistically to reduce peak flow in these patients. The 24 hour mean NO_2 concentrations during the 8 month study period were 39 $\mu g/m^3$ and 48$\mu g/m^3$ for the two cities studied, and peak 24 hour values 91 $\mu g/m^3$ and 95 $\mu g/m^3$.

In a study conducted in Freiburg, Germany, between 1987 and 1990, ambient NO_2 concentrations greater than 40 $\mu g/m^3$ were associated with decreases in lung function in asthmatic children (Moseler et al, 1994). No effects were observed for non-asthmatic children. A 5% decrease in FEV_1%FVC per 10 $\mu g/m^3$ increase in weekly average NO_2 levels above the threshold of 40 $\mu g/m^3$ was observed for the asthmatic group. Yearly mean NO_2 levels ranged from 35 to 42 $\mu g/m^3$.

In a study conducted by Quackenboss et al (1991) the effect of NO_2 on peak expiratory flow in children was examined. The average age of the children was 11.1 yrs and both indoor and outdoor levels of NO_2 were considered. The estimated personal exposure for these children was 19.4 $\mu g/m^3$ for NO_2 and 35.3 $\mu g/m^3$ for PM_{10}. Significant decrements of 40 L/min per 20 $\mu g/m^3$ of NO_2 in PEFR were associated with increasing concentrations of outdoor NO_2 . The most pronounced effect was observed with weekly average levels of NO_2 and it was related to PEFR levels in all times of the day and may reflect a long-term effect of prolonged exposure. This effect was reduced in the evening. The relationship between PEFR and either PM_{10} or $PM_{2.5}$ was significantly less than that to NO_2. No significant effects were observed in healthy children.

A recently reported study from Sydney, as yet only in abstract form, is that undertaken by Jalaludin et al who performed a longitudinal study to investigate the relationship between asthma and air pollution in children living in western and southwestern Sydney as part of the recent HARP project. They concluded that current levels of ambient air pollution in western Sydney could lead to decrements in lung function in a population of children with a history of wheezing. This effect was greater in those children who had positive Histamine challenge responses, however NO consistent association was seen with NO_2. PM_{10} and ozone were also assessed, and when categorised into 'high' and 'low' days (pollution levels), a decrease was seen in the mean deviations in peak expiratory flow rates for the 'high' days compared with the 'low' days, of approximately 1%.

Summary of Data from Epidemiological Studies

The most striking feature from the epidemiological studies (also found in controlled exposure studies) is the inconsistencies with the findings. The mortality studies have indicated that exposure at ambient levels increases daily mortality from respiratory and cardiovascular causes. Effects are seen in all age groups.

Hospital admissions and emergency room visits for cardiovascular and respiratory causes have also been associated with NO_2 levels in various studies in Europe. The results of studies on respiratory illness are not as clear. In general, studies in children have found associations between the incidence and duration of respiratory illness and ambient NO_2 levels. There is little evidence from these studies that the presence of a gas stove in the home increases the risk of respiratory illness although exposure to NO_2 is higher.

Epidemiological studies on lung function response to NO_2 have shown that exposure to ambient levels of NO_2 causes decreases in FEV, FVC and PEF in asthmatic children. Effects in healthy children appear to be minimal.

CONTROLLED EXPOSURE STUDIES

A considerable number of studies have investigated the lung function response to NO_2 in healthy subjects, asthmatics and to a lesser extent, patients with chronic obstructive pulmonary disease (COPD). These results have been quite variable over a wide range of concentrations, which makes the understanding of NO_2 effects in the lung incomplete.

Lung Function, Symptoms and Airway Resistance

At sufficiently high exposures (eg., 2 to 8 ppm), acute exposure to NO_2 can induce statistically significant pulmonary function decrements, symptomatic effects, and increased airway resistance (R_{aw}) in both healthy and sensitive subjects. Airway resistance is defined as the (frictional) resistance to airflow afforded by the airways between the airway opening at the mouth and the alveoli. Although many controlled human exposure studies of healthy individuals conducted at NO_2 concentrations even above 1.0 ppm report negative results, some studies of asthmatics and patients with chronic obstructive pulmonary disease (COPD) observe effects following exposures to NO_2 at concentrations less than 1.0 ppm.

Human exposure studies provide very limited evidence of functional alterations, symptoms, or R_{aw} changes in healthy subjects exposed for short periods (5 minutes to 2 hours) to NO_2 concentrations ranging from 2 to 8 ppm. Most of the studies report no changes in lung function or symptoms; however, increased R_{aw} was observed after short-term exposures of healthy subjects to 5-8 ppm NO_2 (reviewed in Bascom et al, 1996; Sandstrom et al, 1995; Folinsbee, 1992). When healthy subjects were exposed to somewhat lower NO_2 levels (2 to 4 ppm), no changes were reported in either spirometry or R_{aw} (Folinsbee, 1992; Rasmussen et al, 1992). None of the studies investigating healthy subjects exposed to less than 1.0 ppm NO_2 demonstrated any clear responses to NO_2.

In contrast to the lack of effects reported with healthy subjects at lower NO_2 levels, there is some evidence that asthmatics experience symptoms, functional changes, and increased R_{aw} when exposed to NO_2 levels below 1.0 ppm. In one early study of asthmatics, symptoms of respiratory discomfort were experienced by 4 of 13 asthmatics exposed to 0.5 ppm for 2 hours; however, Kerr et al. (1979) concluded that the symptoms were minimal and did not correlate well with functional changes. In several other studies of asthmatics, very small changes in spirometry or plethysmography were reported following acute exposures in the range of 0.1 to 0.6 ppm NO_2 (US EPA, 1995). Hazucha et al. (1982, 1983) found an eight percent increase in specific airway resistance (SR_{aw}) after mild asthmatics were exposed to 0.1 ppm NO_2 at rest. However, this finding is not considered statistically

significant. Bauer et al., (1986) reported statistically significant changes in spirometric response in mild asthmatics exposed for 20 minutes (with mouthpiece) to 0.3 ppm NO_2 and cold air. Avol et al. (1988) found significant changes in SR_{aw} and FEV_1 as a function of exposure concentration and duration for all exposure conditions (ie., exposure of moderately exercising asthmatics for 2 hours to 0.3 ppm and 0.6 ppm NO_2); however, it was concluded that there was no significant effect of NO_2 exposure on these measures of pulmonary function. Exercising adolescent asthmatics exposed (with mouthpiece) to air, 0.12 ppm and 0.18 ppm NO_2 exhibited small changes in FEV_1, but there were no differences in symptoms between air and either of the NO_2 exposures (Koenig et al., 1987a,b). The absence of spirometry or plethysmography changes in studies (Bylin et al., 1985; Linn et al., 1985b; Linn et al., 1986) conducted at higher NO_2 concentrations makes developing a concentration-response relationship problematic.

In healthy subjects, several studies have shown that exposure to 1.5 to 5 ppm NO_2 significantly increases airway resistance (Frampton et al., 1991; Moshenin, 1988; Hazucha et al, 1992). In contrast however, a study by Linn et al (1985) did not show any effects even at concentrations as high as 4 ppm for 75 min with intermittent exercise. Several studies have been unable to demonstrate any significant effects at levels less than 1ppm (Kleinman et al., 1983; Kerr et al., 1979; Hackney et al., 1978; Bylin et al., 1985; Koenig et al., 1985). Bylin et al (1985) detected elevated airway resistance in healthy subjects exposed to a concentration as low as 0.24 ppm without exercise. However, at 0.51 ppm, no effect was observed. Moshenin (1987) observed an increased reactivity to methacholine in healthy subjects exposed to 2 ppm NO_2 for 1 hour.

In a study by Frampton et al (1991) healthy subjects were exposed to NO_2 for 3 hour at 2 week intervals, according to the following protocols: (a) continuous 0.6 ppm NO_2; (b) baseline 0.05 ppm NO_2 with intermittent peaks of 2 ppm, and (3) continuous 1.5 ppm. Subjects underwent intermittent exercise during the exposure period. Pulmonary function was measured before, during and after the exposure and airway reactivity to carbachol was assessed 30 min after exposure. No changes in pulmonary function were observed with any exposure protocol. No alterations in airway reactivity were observed with continuous exposure to 0.6 ppm or intermittent peaks of 2 ppm NO_2. However continuous exposure to NO_2 at 1.5 ppm NO_2 for 3 hours significantly increased airway reactivity.

Patients with COPD also have been used as subjects in NO_2 exposure studies. Due to the hyper-responsiveness of their airways to physical and chemical stimuli, their already compromised lung function, and the poor distribution of ventilation leading to greater NO_2 delivery to the segment of the lung that is well ventilated (thus resulting in a greater local dose), patients with COPD might be expected to experience a heightened response to NO_2 exposures compared to healthy individuals. Early studies (Bascom et al, 1996; US EPA, 1995) found increased R_{aw} with exposure of COPD patients to

1.6 ppm NO_2 or greater. However, in a comparative study of healthy and bronchitic subjects, Von Needing et al. (1980) reported that responses of subjects with bronchitis were similar to those seen in healthy subjects. Inn et al. (1985) investigated effects of a 1-hour exposure to 0.5, 1.0, and 2.0 ppm NO_2 on intermittently exercising patients with emphysema and chronic bronchitis; they found no statistically significant changes in arterial oxygenation, lung function, or symptoms. A study by Morrow and Utell (1989) showed that no effect on pulmonary function or respiratory symptoms occurred on exposure to 0.3 ppm NO_2 in healthy young and elderly patients. In asthmatics, no significant reductions in lung function were observed after exposure to NO_2. However in elderly patients with COPD, small but significant reductions in lung function were observed during light to moderate activity at 0.3 ppm NO_2. These authors concluded that this level of NO_2 is probably close to the minimally effective exposure level for susceptible groups.

Effects of NO_2 on healthy elderly subjects and elderly subjects with COPD have been investigated by Morrow et al, (1992). Over a 2 yr period subjects were exposed for 4 hours per day for 5 day protocol to either NO_2 or air with intermittent exercise. During intermittent light exercise, subjects with COPD demonstrated progressive decrements in FVC and FEV_1 on exposure to 0.3 ppm NO_2, but not with air. Subgroup analyses suggested that responsiveness to NO_2 decreased with the severity of COPD. In elderly normal subjects, mean responses to air and NO_2 were virtually identical. NO_2-induced reduction in FEV_1 was greater among smokers than never smokers.

A study by Devalia et al., (1994), has shown that exposure of asthmatics to 400 ppb NO_2, or NO_2 combined with SO_2, for 6 hours does not significantly affect FEV_1 or FVC. The combination of NO_2 and SO_2 however was found to enhance the airway response to the allergen Dermatophagoides pteronyssinus. In response to this study Anto and Sunyer (1995) have suggested that exposure to the complex mixture of pollutants that are present in the urban atmosphere could induce larger inflammatory and functional changes than those reported in the study by Devalia et al., (1994). Thus the effect of air pollution on allergic asthma may be even larger than that seen in experimental studies. These authors suggest that NO_2 could influence asthma in two ways: (a) by decreasing the threshold for allergen exposure needed to develop sensitisation and allergic asthma; and (b) by increasing morbidity of existing asthma.

The effect of sequential exposure to NO_2 and O_3 on the lung function of healthy women has shown that the provocative dose of O_3 required to cause a 10% reduction in FEV_1 ($PD_{10}FEV_1$), was significantly reduced when subjects were exposed to 0.6 ppm NO_2 as opposed to clean air (Hazucha et al, 1994). Subjects were exposed on day one for 2 hour to clean air followed 3 hour later by a 2 hour exposure to 0.3 ppm O_3. Two weeks later the subjects underwent a similar protocol with 0.6 ppm NO_2 substituted for clean air. The median $PD_{10}FEV_1$ in these subjects was reduced from 5.6 mg/ml to 1.7 mg/ml

compared with the air-O_3 sequence. In contrast however, no effect of pre-exposure to NO_2 was observed for airway resistance. Exposure to NO_2 alone had no effect on the lung function parameters in these subjects.

NO_2 has been found to induce activation of cells in subjects with mild asthma compatible with enhancement of airway inflammation; lung function parameters and cellular composition of bronchoalveolar lavage (BAL) fluid were not markedly affected (Jorres et al, 1995). In this study subjects were exposed to 1 ppm NO_2 with intermittent exercise for 3 hours. Bronchoscopy with BAL was performed 1 hour after each exposure, and on a third day after exposure. Prostanoids, leukotrienes and histamine were analysed in BAL fluid, and the cellular composition of the fluid was assessed. In the asthmatic subjects, NO_2 induced a small drop in FEV_1, however differential cell counts in BAL fluid did not reveal significant effects of NO_2. Levels of 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) were decreased, and levels of thromboxane B_2 (TxB_2) and prostaglandin D_2 (PGD_2) in BAL fluid were increased after NO_2 compared to filtered air exposure. Prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), histamine and leukotriene levels did not change significantly. The normal subjects showed no change in lung function parameters and a small increase in TxB_2 after breathing NO_2. PGD_2 and TxB_2 are inflammatory mediators associated with bronchoconstriction, while 6-keto-$PGF_{1\alpha}$ is associated with bronchodilatation.

In summary, in healthy individuals, even very high acute NO_2 exposures do not appear to cause pulmonary function effects, symptoms, or increases in R_{aw}. The current database does, however, show that small pulmonary function changes have occurred in asthmatics at low, but not high (ie., up to 4 ppm), NO_2 concentrations. Although the observed effects were noted in different studies, no plausible explanation is offered to account for this lack of a concentration-response relationship. The most significant responses to NO_2 that have been observed in asthmatics have occurred at concentrations between 0.2 and 0.5 ppm. Patients with COPD experience pulmonary function changes with brief exposure to high concentrations (5 to 8 ppm for 5 minutes) or with more prolonged exposure to lower concentrations (0.3 ppm for 3.75 hours).

Increased Airway Responsiveness

There is little, if any, convincing evidence that healthy individuals experience increases in airway responsiveness when exposed to NO_2 levels below 1.0 ppm. However, studies of asthmatics have reported some evidence of increased airway responsiveness caused by acute exposure to NO_2 in the range of 0.2 to 0.3 ppm.

Responsiveness of an individual's airways is typically measured by evaluating changes in airway resistance or spirometry following challenge with a pharmacologically active chemical (eg., histamine, methacholine, carbachol), which causes constriction of the airways. Airway hyper-responsiveness is reflected by an abnormal degree of airway narrowing caused primarily by airway smooth muscle shortening in response to nonspecific stimuli. Asthmatics experience airway hyper-responsiveness to certain chemical and physical stimuli and have been identified as one of the population subgroups which is most sensitive to acute NO_2 exposure.

Evidence of increased airway responsiveness in normal adults has been reported in very few studies. Mohsenin (1988) found increased airway responsiveness to methacholine following exposure to 2 ppm NO_2 for 1 hour at rest. Frampton et al. (1991) reported statistically significant airway responsiveness following a 3-hour exposure of healthy subjects to 1.5 ppm NO_2 and carbachol challenge, but no increase in airway responsiveness was reported with exposure to 0.6 ppm NO_2. In one study (Hazucha et al., 1994), airway responsiveness, which was subsequently induced by a 2-hour exposure to 0.3 ppm O_3, was augmented by a 2-hour pre-exposure to 0.6 ppm NO_2. None of these studies, however, provide clear evidence of increased airway responsiveness in normal individuals when exposed only to NO_2 at concentrations of 1 ppm or lower.

There is evidence that exposure of mildly allergic asthmatic patients to NO_2 levels below 1 ppm may cause increased airway responsiveness. Several controlled exposure studies (US EPA, 1995; Bylin et al., 1985; Koenig et al., 1985) of asthmatics showed no significant effect on responsiveness at very low NO_2 concentrations of 0.1 to 0.12 ppm. Using a mouthpiece and somewhat higher exposures of 0.3 ppm NO_2, Bauer et al. (1986) reported a statistically significant response to NO_2 after 20 minutes rest followed by 20 minutes of exercise (30 L/min); all had elevated response to cold air broncho-provocation. A subsequent study (Morrow and Utell, 1989), using some of the same subjects in the same laboratory, showed no change in lung function, symptoms, or carbachol reactivity following exposure to 0.3 ppm NO_2. It is important to note, however, that the Morrow and Utell (1989) study was a chamber study; thus, the difference in exposure mode (mouthpiece versus chamber) could account for the significant difference in the study results. Studies which investigated concentration-response relationships for exposures of $\leq$ 0.6 ppm NO_2 (Roger et al., 1990; Bylin et al., 1985, 1988; Avol et

al., 1988) found no significant changes in spirometry or airway reactivity as a result of NO_2 exposure. Even for exposures to 3.0 ppm (Linn et al., 1986) and 4.0 ppm NO_2 (Linn and Hackney, 1984), no effects of NO_2 on SR_{aw}, symptoms, heart rate, or skin conductance were reported in exercising asthmatics.

A meta-analysis of twenty studies of asthmatics and 5 studies of healthy subjects by Follinsbee (1992) indicated that exposure to NO_2 at levels between 0.2 to 0.3 ppm causes increased airway responsiveness in healthy and asthmatic subjects but that exercise may modify this response in asthmatics. This analysis raises a few questions with regard to the influence of exercise on the observed effects of NO_2. The response of asthmatics to NO_2 was primarily due to those observed at resting exposure. Only a further 10% change occurred with exercise even though the total volume of air inhaled and the tidal volume is increased with exercise. Because NO_2 at these levels does not appear to cause airway inflammation and the increased airway responsiveness appears fully reversible, implications of the observed increases in responsiveness remain unclear. It has been hypothesised that increased nonspecific airway responsiveness caused by NO_2 could lead to increased responses to a specific antigen; however, there is no plausible evidence to support this. Follinsbee proposed several mechanisms by which this pattern could be explained: (a) that exercise interferes with the mechanism causing increased airway resistance in NO_2 exposed individuals; (b) that although exercise increases the overall uptake of NO_2 the relative uptake in the tracheobronchial region may be reduced; (c) that NO_2 exposure may cause a direct relaxing effect on the airway smooth muscle brought about by the formation of nitrates in the airway lining fluids; and (d) that a low exposure dose of NO_2 may induce airways responsiveness that is blocked by some other action of NO_2 at higher concentrations.

There are indications that asthmatics are more susceptible to increased airway reactivity to NO_2 than healthy subjects. Bauer et al (1986) found that exposure to 0.30 ppm NO_2 caused airways hyper-responsiveness to exercise and cold air provocation. In a preliminary study of 13 male asthmatics, decreases in FEV_1, FVC and SR_{aw} were observed after moderate exercise in 0.3 ppm NO_2 (Roger et al, 1990). An extension of this study looking at the concentration dependence of this response failed to show any correlation between NO_2 levels and pulmonary function (Roger et al., 1990). There were also no significantly different changes observed in respiratory symptoms between clean air and NO_2 exposures. The conclusion of these authors was that on average mild asthmatics are not sensitive to low levels (< 0.6 ppm) of NO_2 as measured by pulmonary function, respiratory symptoms and airway responsiveness to methacholine.

A study by Jorres and Magnussen (1991) found similar results to those of Roger et al (1990). Exposure of mild and stable asthmatics with normal airway tone to 0.25 ppm NO_2 for 30 min including 10 min exercise, had no effect on the airway response to methacholine. In addition, no effect was observed on exercise-induced bronchoconstriction. These authors suggest that the differing results which have been observed on the effect of exposure to low level NO_2 on airway

responsiveness in asthmatics, are likely to depend on the severity of the disease, baseline airway calibre, and the stimulus for evaluating airway hyper-responsiveness.

A further study investigating the effect of nitrogen dioxide on airways responses to inhaled allergen (Tunnicliffe et al., 1994) showed that exposure to 400 ppb NO_2 increased asthmatic response to house dust mite (HDM) allergen. The observed effect was small but resulted from a single exposure rather than repeated exposure. These authors suggest that NO_2 may act as a permissive agent in allowing other factors to exacerbate asthma or that underlying factors such as allergy or subclinical inflammation may be a prerequisite for the expression of any detrimental effects of the gas. Also these authors have suggested that the oxidative capacity of NO_2 could affect the integrity of cell membranes, thereby increasing the permeability of the bronchial epithelium to inhaled allergen, effectively increasing its delivered dose. This has been shown to occur in cultured human bronchial epithelial cell monolayers exposed to 400 ppb and 800 ppb NO_2 over short periods; there is also an increase in inflammatory cytokines granulocyte-macrophage colony-stimulating factor, interleukin-8, and tumour necrosis factor α, which may allow potentiation of the allergic response for the same presented dose of allergen.

In an earlier study by Jorres and Magnussen (1990), exposure of mild asthmatics to 0.25 ppm NO_2 for 30 min enhanced airway responsiveness to hyperventilation of SO_2, without altering airway tone, whereas short-term exposure with low concentrations of SO_2 did not. The authors suggest that their findings may point to the possibility of interactions between pollutants rather than NO_2 enhancing airway responsiveness to other pollutants. A further study investigating the effects of NO_2 on the airway responsiveness to SO_2 in asthmatics found that exposure to 0.3 ppm NO_2 for 30 min has no effect on pulmonary function or respiratory symptoms and does not potentiate airway responsiveness to SO_2 (Rubinstein et al, 1990).

In summary, there is some evidence that acute exposure to NO_2 may cause an increase in airway responsiveness in asthmatic individuals. This response has been observed only at relatively low NO_2 concentrations, mostly in the range of 0.2 to 0.3 ppm NO_2. However, the above findings, taken as a whole, do not provide any clear quantitative conclusions about the health effects of short-term exposures to NO_2.

Toxicology

The toxicology of NO_2 has been well studied and the subject of many reviews (Samet and Utell, 1990; Berglund et al, 1993; Sandstrom, 1995) . Nitrogen dioxide is not very soluble in tissues and removal of inhaled NO_2 in the upper airway is limited. Dosimetric studies show that most inhaled NO_2 is retained in the lungs and deposited primarily in the large and small airways, with little deposition in the alveoli (US EPA, 1995; Bauer, 1986). Because of its low degree of tissue solubility, NO_2 not only reacts with the alveolar epithelium, but with the interstitium and endothelium of the pulmonary capillaries (Mustafa, 1978). Inhaled NO_2 is thought to combine with water in the lung to form nitric (HNO_3) and nitrous (HNO_2) acids, and this is thought to be important in terms of the toxicity of NO_2 (Sandstrom, 1995). Substantial uncertainty remains concerning the reactions of NO_2 with tissue.

Oxidant injury has been postulated to be the principal mechanism through which NO_2 damages the lung (Mustafa, 1978). These mechanisms have been suggested to involve lipid peroxidation in cell membranes and various actions of free radicals on structural and functional molecules. Particularly strong free radicals are formed when NO_2 oxidises lecithin in cell membranes or surfactant, and by interaction with haem (Sandstrom, 1995). Hydrogen abstraction dominates the reaction of unsaturated fatty acid with NO_2. Secondary reactions of fatty acid radicals with oxygen lead to peroxyl radicals. Peroxyl radicals initiate a chain reaction of peroxidation with membrane lipids (Menzel, 1994). At high concentrations NO_2 causes extensive lung injury in animals and humans (US EPA, 1995). Fatal pulmonary oedema and bronchopneumonia have been reported at extremely high concentrations; lower concentrations are associated with bronchitis, bronchiolitis and pneumonia (US EPA, 1995). Sustained lower level exposures of animals are associated with emphysematous enlargements of the terminal airspaces (Bascom et al., 1996).

A study by Rasmussen et al., (1992) has found that exposure to 2.3 ppm NO_2 for 5 hours caused a 14% decrease in serum glutathione peroxidase activity with indications of a 22% decrease in alveolar permeability. These decreases were observed 24 hour and 11 hour respectively after exposure to NO_2 supporting the suggestion that the human response to NO_2 is delayed. The changes in alveolar permeability reflects changes in the most peripheral parts of the lungs, the area that has been shown from animal experiments to be the main target area for NO_2. No indications of mucous membrane irritation or decreased lung function were observed during or after NO_2 exposures.

Experimental evidence also indicates that NO_2 exposure adversely affects lung defence mechanisms (Morrow, 1984; Gardner, 1984). Lung defence mechanisms against inhaled particles and gases include aerodynamic filtration, mucocilliary

clearance, particle transport and detoxification by alveolar macrophages, and local and systemic immunity. In experimental models, NO_2 reduces the efficacy of several of the lung defence mechanisms; its effects on mucocilliary clearance, the alveolar macrophage and the immune system have been demonstrated (US EPA, 1996).

Exposure to 4 ppm has been shown to increase airway responsiveness in guinea pigs after 3 days (Kobayashi and Shinozaki, 1992). This transient hyper-responsiveness was inhibited by a specific inhibitor of thromboxane synthetase, OKY 046, indicating that thromboxane A_2 may play an important role. Prolonged exposure for 7 days to NO_2 did not induce airway hyper-responsiveness. NO_2 has also been shown to induce eosinophilia and mucosal injury in the nose of the guinea pig (Ohashi et al., 1994). Exposure to 3 ppm NO_2 for 6 hours a day for 6 weeks resulted in decreased ciliary activity and slight eosinophil accumulation on the epithelium and submucosal layer. More serious pathologies were observed in guinea pigs exposed to 9 ppm NO_2.

Douglas et al (1995) have shown that exposure of rabbits to NO_2 for 2 hours a day, 5 days a week from birth to 3 months of age, has no effect on airways responsiveness in rabbits sensitised to house dust mite antigen at birth. No effect was observed on pulmonary function in rabbits exposed to either NO_2.

Host Defence and Responses to Infection

Animal Studies

Animal exposure studies have been used extensively to examine effects of NO_2 exposure defence against infection. Exposure to NO_2 followed by inhalation challenge with a pathogenic organism has been the experimental model used most extensively. A series of animal infectivity studies has shown that exposure to NO_2 can increase susceptibility to respiratory infection and result in microbial-induced mortality. These studies involve exposure of animals to varying concentrations and durations of NO_2 followed by exposure to an aerosol laced with an infectious agent (eg., bacteria or virus). Although the lowest acute (2-hour) exposure to affect bacteria-induced mortality was 2.0 ppm, subchronic exposures to NO_2 concentrations as low as 0.5 to 1.0 ppm have increased both bacteria-induced and influenza-induced mortality (US EPA, 1995; Bascom et al, 1996). These as well as numerous other studies (reviewed in US EPA, 1995; Bascom et al, 1996) have provided support for the contention that NO_2 increases microbial-induced mortality by impairing the host's ability to defend the respiratory tract from infectious agents, thereby increasing susceptibility to viral, mycoplasma, and bacterial infections. Using susceptibility to respiratory infection as an index, Gardner et al. (1977a,b) and Coffin et al. (1977) concluded that incidence of mortality was significantly more influenced by concentration of NO_2 than by duration of exposure. These studies, however, used a large range of exposure concentrations (0.5 - 28 ppm), beginning above typical ambient concentrations. In the ambient range of exposures, time may be a more important influence than concentration. However, there was no data showing clearly the effect of time on effects of long-term, low-level exposures representing ambient exposure levels. In the urban air, the typical pattern of NO_2 is a low-level baseline exposure on which peaks are superimposed. When the relationship of the peak to baseline exposure and of enhanced susceptibility to bacterial infection was investigated, the results indicated that no simplistic concentration times time relationship was present, and that peaks had a major influence on the outcome (US EPA, 1995). Animal infectivity studies have offered evidence which indicate that mice exposed to baseline plus short-term peaks were more susceptible to respiratory infection than either those exposed to control or background levels of NO_2. This research also indicated that the pattern of NO_2 exposure had a major influence on the response.

Studies in mice have shown the following results (Gardner, 1984) :
(a) NO_2 exposure increased mortality from a subsequent bacterial challenge;
(b) peak exposure levels were more closely associated with mortality than duration of exposure when the product of concentration x time was held constant; and

(c) increased mortality was observed with NO_2 exposures as low as 0.5 ppm for 9 weeks. Several other studies have attempted to elucidate the mechanisms by which NO_2 exposure renders animals more susceptible to bacterial challenge.

In a study by Goldstein et al (1973) using radiolabelled *Staphylococcus aureus* as an infectious challenge, exposure to NO_2 at levels as low as 2.3 ppm for 17 hours decreased bacterial killing when compared with air exposure, but did not alter bacterial clearance as determined by decrease in intrathoracic radioactivity over time. NO_2 has also been found to decrease killing of S. aureus in the lung at (4 ppm) compared with *Proteus mirabilis* (10 ppm). Because *S. aureus* is primarily cleared by alveolar macrophages whereas P. mirabilis is cleared by both macrophages and neutrophils, support was provided for the hypothesis that, in the murine model, NO_2 primarily affects alveolar macrophage antimicrobial function (Bascom et al., 1996).

A study by Rose et al., (1989), has shown that exposure to 5 ppm NO_2 enhances the susceptibility of the lower respiratory tract in mice to both primary infection and reinfection with a virus. This susceptibility is based, at least in part, on NO_2-associated alterations in pulmonary macrophage function and lymphocyte anamnestic responses to viral antigen. Although the exposure threshold necessary to produce these effects on viral susceptibility is considerably greater than ambient levels of NO_2, exposure to this level of NO_2 alone produced no biochemical or histologic indications of major pulmonary injury. Therefore, exposure to a concentration of NO_2 that has no observable effects on lung structure is nevertheless capable of predisposing the respiratory tract to infection with a virus.

Human Studies

Relatively few controlled-exposure studies have been conducted using human subjects exposed to NO_2 and infectious agents. One such study (Goings et al., 1989) examined the effects of NO_2 on pulmonary host defence systems using live attenuated influenza virus and reported a non-statistically significant trend toward elevated rate of infection. Similarly, Frampton et al. (1989a) reported a trend for less effective inactivation of virus by alveolar macrophages taken from subjects exposed continuously to 0.6 ppm NO_2 for 3 hours, although no effects were reported in those exposed continuously to 0.05 ppm with three 15 minute 2.0 ppm spikes with exercise. In a related investigation, Frampton et al. (1989b) found that 3 hours of exposure to 0.60 ppm NO_2 may transiently increase levels of antiprotease alpha-2-macroglobulin in lung lavage fluid and thereby may alter alveolar macrophage defenses against infection. Although these studies are suggestive, they do not provide clear evidence that NO_2 increases susceptibility of humans to respiratory infection.

The results of a study by Kulle and Clements (1987) indicated that NO_2 may play a role in the susceptibility of adults to respiratory virus infections. This chamber study looked at the results of exposure to NO_2 and attenuated influenza A virus over a three year period. Subjects were exposed for 3 days to either NO_2 or clean air. At the end of the second exposure day subjects were inoculated intra-nasally with the influenza A virus. On each of the 4 days post inoculation, the subjects were examined for symptoms and had nasal washes to detect virus replication. Serum and nasal washes were collected one week prior and 3-4 weeks after virus administration to measure systemic and local antibody responses to the virus. The nitrogen dioxide concentration to which the subjects were exposed was 1 ppm in year 3, 2 ppm years 1 and 3, 3 ppm in year 2. The overall results of this study were inconclusive, however, there was some evidence in the third year of the study that exposure to 1 to 2 ppm NO_2 may enhance the susceptibility to virus infection in individuals who have previously been infected with similar viruses.

The weight of evidence provided by animal toxicology and human exposure studies supports the contention that NO_2 impairs the ability of host defence mechanisms to protect against respiratory infection. Although some of the health endpoints may not be valid for humans (eg., increased mortality), there are many shared mechanisms between animals and humans which support the hypothesis of association between NO_2 exposure and increases in respiratory symptoms and illness reported in the epidemiological studies.

TABLE 1

Sensitive Subpopulations

Elderly, asthmatics, individuals with respiratory and/or cardiovascular disease.

Dose Response Relationships

The dose response curves for NO_2 and respiratory illness do not appear to be linear.

Epidemiological Studies

HEALTH ENDPOINT	STUDY POPULATION	LOWEST LEVEL AND AVERAGING TIME	UPPER LEVEL AND AVERAGING TIME
Mortality	Elderly	88μg/m³ mean 1 hour	339 μg/m³ max 1 hour
	Individuals with cardiovascular disease	57.2 μg/m³ mean 1 hour 69 ppb mean daily	370 μg/m³ max 1 hour
	Children < 5 yrs	35.1 μg/m³ mean 24 hour	
Hospital Admissions	Individuals with Respiratory Disease	54 μg/m³ mean 24 hour	102.5 μg/m³ mean 24 hour
	Asthmatics	13.4 μg/m³ mean 24 hour 73.8 μg/m³ mean max 1 hour	102.4 μg/m³ 24 hour mean 202.7 μg/m³ 99th percentile 1hour max
	Individuals with cardiovascular disease	102.4 μg/m³ 24 hour mean	
Respiratory Illness	General	0.043 ppm mean 24 hour	0.083 ppm mean 24 hour
	Children < 12 yrs	6.5 μg/m³ yearly average 49 μg/m³ daily max	22.6 μg/m³ yearly average 502 μg/m³ daily max 98 μg/m³ mean 24 hour max.
	Children < 5yrs	25 μg/m³ annual average	51 μg/m³ annual average
Lung Function	General	0.062 ppm mean 24 hour 0.098 ppm 24 hour 90th percentile	0.109 ppm mean 24 hour 0.242 ppm 24 hour 90th percentile

HEALTH ENDPOINT	STUDY POPULATION	LOWEST LEVEL AND AVERAGING TIME	UPPER LEVEL AND AVERAGING TIME
	Children	<0.05 ppm 19.4 μg/m³ weekly average (personal exposure)	
	Asthmatics	39 μg/m³ mean 24 hour 91 μg/m³ 24 hour max	48μg/m³ mean 24 hour
	Asthmatic Children	40 μg/m³ weekly average	

Controlled Exposure Studies

HEALTH ENDPOINT	STUDY POPULATION	LOWEST LEVEL AND AVERAGING TIME	UPPER LEVEL AND AVERAGING TIME
Lung Function	Individuals with COPD	0.3ppm for 4 hours	5 to 8 ppm for 5 mins
	Asthmatics	0.12 ppm	0.18 ppm
Airway Resistance	Healthy Subjects	1 ppm 1.5 ppm for 3 hours	8 ppm
	Asthmatics	0.1 ppm	
Respiratory Symptoms	Asthmatics	0.5 ppm for 2 hours	
Airway Inflammation	Asthmatics	1 ppm for 3 hours	
Airway Responsiveness	Healthy Subjects	1 ppm 3 hours	
	Asthmatics	0.2 ppm 20 mins	0.3 ppm 20 mins
Increased Sensitivity To Allergen	Asthmatics	0.4 ppb	
Increased Sensitivity to So_2 and O_3	Asthmatics	0.3 ppm 30 min (SO_2)	
	Healthy Subjects	0.6 ppm 2 hours (O_3)	
Host Defence: Infectivity	Healthy Subjects	0.6 ppm 3 hours	

A Review on Existing Health Data on Six Pollutants
Prepared by Dr Jonathon Streeton for the National Environment Protection Council

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APPENDIX 4 -
HEALTH EFFECTS OF OZONE

SUMMARY [#]

Ozone is a highly irritant substance which has significant effects at various levels of the respiratory tract from the nasal passages to the alveolar epithelial membrane, now well described by many authorities.

There is strong supportive evidence of clinical, epidemiological and controlled exposure associations with ozone at ambient levels normally encountered in Australian cities. These exposures result in a range of acute health effects which include minor changes in lung function, increasing symptoms consistent with upper and lower airway irritation, leading to an increased requirement for additional medication, increased requirement for medical services such as attendance at medical surgeries, hospital casualty departments, and hospitalisation.

There is also evidence of a slight but definite increase in mortality, chiefly from cardiovascular causes, particularly in the elderly, following ozone exposure.

Population studies recently undertaken in Sydney which assessed various health outcomes including morbidity and mortality confirmed previous assumptions that the literature on the adverse health effects of ozone observed in North America and Europe is reproducible in Australia, and there is no reason why similar response patterns would not be observed in other larger Australian cities.

There is consistent evidence to suggest that there are specific subgroups within the population which are more susceptible to the adverse health effects of ozone, in particular, asthmatics. In addition, there is an increasing body of literature which details the various interactions between the pollutants ozone, nitrogen dioxide, particles, and to a lesser extent in the Australian context, sulfur dioxide. In particular, there is robust statistical data which supports enhancement of the effects of ozone, as a result of prior or concurrent exposure to particles, nitrogen dioxide, airborne allergens, and to sulfur dioxide, collected in a wide range of environments in many countries. Meteorological factors such as temperature have also shown influence. The coherence of the relationships of pollutants and the many associations of effects, including mortality events leaves little doubt as to the validity and the strength of assumptions of causality.

Animal toxicological evidence is supportive of the human clinical observations which suggest that the primary mechanism of action of ozone is the induction of vigorous inflammatory responses, which in turn lead on to acute adverse

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[#] Reviewed and edited by Dr. Jonathan A. Streeton, FRACP, of Jonathan A. Streeton Pty. Ltd.

respiratory events. Certainly in the context of short-term exposures, it is proper to conclude that the associations are causal.

In the context of longer term or chronic exposures, the epidemiological and experimental evidence is much less certain. In experimental animals, it is possible to demonstrate the development of an inflammatory bronchiolitis at the level of the respiratory bronchioles, however in human subjects, there are only suggestions of adverse response patterns and then usually only in the context of high levels of chronic exposure with worsening asthma, increased rates of functional decline in adults, impairment of normal lung growth in children, and possible changes in pulmonary immunological function especially in children. Considerable experimental work remains to be undertaken in this regard.

Previously, it has routine practice to express ozone goals or guidelines in terms of short exposures, generally of 1 hour; and in terms of a longer period of exposure, generally 8 hours. This approach ignores however the natural time frame for the evolution of the cycle of photochemical reactions in the atmosphere which normally take some 4 to 6 hours to develop during daylight hours. On the other hand, the evolution of the human inflammatory response patterns occurs over a much shorter period, usually only a few hours (1 – 3 hours), and a strong argument can be made for having the primary goal or guideline maintained at a shorter interval to allow suitable control of the acute clinical responses, particularly in the more susceptible groups such as asthmatics, or exercising but otherwise healthy young adults.

No threshold exposure levels can be identified for ozone.

There is a monotonic relationship between increasing ozone concentration and adverse health effects. It is therefore not possible at this time to define either a No Observed Effect Level (NOEL), or a Lowest Observed Adverse Effect Level (LOAEL) for ozone.

Suggestions for suitable protective goals, standards or guidelines must therefore be based on directly observed measurements, whilst keeping in mind that natural factors including local vegetation and the proximity of the sea are significant sources of ozone, quite apart from ozone derived from anthropogenic sources. These observations are emphasised when it can be demonstrated that outdoor workers, such as those described recently from British Columbia, can be shown to lose significant functional capacity over the summer working period at ozone levels which are barely above background levels. A short-term goal or guideline clearly would not be protective in this context.

Therefore it is suggested that the averaging period for the primary goal or guideline for ozone should be (6 -) 8 hours on a rolling basis over daylight hours, with ozone levels for that period averaging between 0.05 - 0.06 ppm (50 - 60 ppb),not to be exceeded. A goal or guideline of this order

should give adequate protection for those healthy individuals required to exercise outdoors over longer intervals of several hours, or indeed for the full working day.

A shorter term goal or guideline should be considered to achieve adequate protection for the clinically compromised in the community as a asthmatics and also young children who may be also exposed to other irritants such as indoor nitrogen dioxide. The margin however between clinical effect and background is very narrow. It is suggested therefore that a short-term 1 hour goal or guideline should be only marginally greater than the longer term primary goal or guideline, and ozone levels in the range 0.08 - 0.09 ppm (80 - 90 ppb), not to be exceeded, are suggested for consideration in order to achieve protection of the more susceptible individuals in the community.

GENERAL REVIEW [#] [*]

Ozone (O_3) is a secondary air pollutant formed by reactions of the primary pollutants, oxides of nitrogen (NO_x) and hydrocarbons in the presence of sunlight. These primary pollutants arise mainly from motor vehicle emissions, stationary combustion sources and industrial and domestic use of solvents and coatings. Ozone enters the human body through the respiratory tract where it reacts with polyunsaturated fatty acids , various electron donors (eg. ascorbate and Vitamin E), and the thiol, aldehyde, and amine groups of low molecular weight biochemicals and proteins.

The mechanisms of the biochemical and physiological effects of human exposure to O_3 remain the subject on intense research. These mechanisms include the direct action of O_3 on macromolecules in the lungs, the reaction of secondary biochemical products resulting from the generation of free-radical-precursor molecules, and the release of reactive oxygen intermediates and proteinases associated with the activities of inflammatory cells that subsequently infiltrate into lungs already damaged by free radical O_3^- (US EPA 1996b, p 26).

In addition to the lower airway responses just described, there is now an emerging body of data which would suggest that the primary impact region for ozone in the human respiratory tract may well be the nasal airways. Both human and animal studies in recent years indicate that the transitional zone epithelium in the nasal passages appears to be specifically susceptible to ozone, with resultant release of inflammatory mediators, which in turn set in train a series of inflammatory responses further down into the lower airways.

Evaluation of health-related data

The health effects of O_3 have been widely studied and have been the subject of many reviews (US EPA 1996a, 1996b, 1996c;Bascom et al 1996;Guest et al 1996;Health Canada 1996; Bromberg and Koren 1995; Woodward et al 1995; Bates 1995a, 1995b; Koren and Bromberg 1995; Koenig 1995; Leikauf et al 1995; Jakab 1995; Balmes 1993; Fryer and Jacoby 1993; Lippmann 1993; Victorin 1992; DoH 1991: Streeton 1990; WHO 1987).

In addition, the adverse health effects of mixtures of pollutants, including ozone, have been reviewed by a number of authors, generally as single pairs of pollutants one of which is ozone, but a useful general review of the currently

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[*] Ozone concentrations are generally referred to in parts per million (ppm). 1ppm = 1000 ppb = $2000\mu g/m^3$. At $0°C$ and 101.3 kPa, the exact conversion for 1 ppm is $2140 \mu g/m^3$, however as research findings are generally reported in ppm without statements of the ambient temperatures or pressures applying at the times of measurement, the units stated in the cited reports are repeated without correction in this assessment.

identified effects of combined pollutant mixtures can be found in *"Health Effects of Exposures to Mixtures of Air Pollutants"* (DoH 1995).

Controlled human exposure studies have shown three types of lung response to acute O_3 exposures:
1. irritative cough and substernal chest pain on deep inspiration;
2. decrements in FVC and FEV_1 due principally to decreased inspiratory capacity rather than airways obstruction; and
3. neutrophilic inflammation of the airway sub-mucosa accompanied by increased levels of mediators and proteins in bronchoalveolar lavage (BAL) fluid.

The level of decrease in pulmonary function does not appear to be associated with the level of inflammatory response. Other demonstrated effects include decreased athletic performance, increased epithelial permeability of the airways, increased non-specific airways reactivity and altered mucociliary clearance. Epidemiological studies have provided findings consistent with those from controlled experimental settings (Table 1 of this Appendix, adapted from Guest et al, 1996).

Range of impacts on human health (sub-clinical and clinical) on general populations and on susceptible sub-groups:

Exposure to low levels of oxidant pollutants causes tissue injuries in the region of the bronchiolar-alveolar duct junction of the lung. Acute tissue reactions after exposures of several days include epithelial inflammation, interstitial oedema, cell hypertrophy, and the influx of macrophages, observed in humans and other species. While human tissue injury may be progressive with prolonged exposure (Crapo et al 1992) the existence of chronic health effects that result from long-term exposure to low concentrations of ozone remains controversial.

In a large number of controlled human studies, significant impairment of pulmonary function has been reported, usually accompanied by respiratory and other symptoms (see Table 1 of this Appendix). The severity of these symptoms parallels the impairment of pulmonary function both in magnitude and time-scale (Beckett 1991). Pulmonary function changes have now been repeatedly demonstrated to occur in exercising subjects exposed to ozone concentrations of 0.08 ppm or less for 6 - 8 hours (Brauer et al 1996; Folinsbee et al 1988). The magnitude and duration of these exposures are similar to exposures which occur during the afternoons of the warmer months, in and around many cities of the world, and certainly in most, if not all larger Australian cities (Salisbury and Ferrari 1997).

TABLE 1
Associations of Ozone with health-related events in humans

Ozone conc^n.(ppm)	Exposure duration	Health event	References
Epidemiological studies			
< 0.085	Summer months whole day	Reduced lung function in farm workers	Brauer 1996
0.10 - 0.16	Summer months	Death (2.5% increase/0.01ppm)	Moolgavkar 1995
< 0.12 (daily 1-hour max. in ambient air)	Days - weeks	Reduced lung function in children, adolescents and adults	Kinney 1989 Krzyzanowski 1992
		Exacerbations of asthma	Whittemore 1980 Holguin 1985
		Respiratory symptoms	Schwartz 1992
Controlled-exposure (chamber) studies			
≥0.08	6.6 hours	Reduced lung function	Folinsbee 1988 Horstmann 1990
> 0.10	1-3 hours	Increased airway responsiveness	Folinsbee 1989
		Airway inflammation	Devlin 1991

Impaired respiratory function can therefore occur at exposure levels similar to, or less than, the current Australian air quality goal (0.10 ppm, averaged over one hour, as revised by the NHMRC in 1995). The range of individual susceptibility is wide however (Woodward et al 1995; Bates 1995b), and must be allowed for any consideration of safe protective ranges.

Between a daily maximum one-hour average ozone concentration of 0.05 and 0.10 ppm, WHO classifies the overall effect on human health as 'mild' (World Health Organisation 1992) In this range of ozone exposures, eye, nose and throat irritation would probably occur in a sensitive minority, with an approximate average decrement of 5% in the forced expiratory volume (one second) in the whole population, increasing to a 10% loss in the most sensitive 10%. A minority of adults may experience some chest tightness and cough. Some athletes could note a slight reduction in peak performances at this level of exposure to ozone.

The most recent review available (USEPA 1996b, p31). has not identified effects at lower concentrations of ozone than the range classified by WHO

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above. For short-term exposures of 1-2 hour, subjects exposed to higher O_3 concentrations (eg. >0.25 ppm) during intermittent heavy exertion tend to experience rapid responses that suggest that a plateau has been reached. However, lower O_3 concentrations with lighter exertion tend to induce responses which progress slowly and may not reach a plateau during the period of exposure. McDonnell and Smith (1994) plotted predicted mean decrements in FEV1 versus time, with intermittent moderate exertion during a 6.6 hour exposure; they found not response plateaus at 0.08, 0.10. or 0.12 ppm O_3 during the first 3 hour, but did not show plateaus developing at each concentration during the latter portion of the exposure.

Ozone may sensitise persons with asthma to other agents that induce bronchospasm (Molfino et al, 1991; Koenig et al, 1990). Therefore, an air quality goal to protect persons with asthma and an atopic tendency may require greater stringency than needed for the remainder of the population (Woodward et al, 1995) Little information is available on long-term effects, a critical gap for public health considerations. The chronic effects may include lung structure abnormalities, resulting in increased rates of respiratory disease, hospital admission and mortality (Lippmann 1993).

Identification of dose-response relationship and threshold for the effects on human health

<u>Dose-response</u>

The most consistent indication of a dose-response relationship comes from panel studies of adolescents in summer camps in the United States (USEPA 1996b p32; Bates 1995b). .Exposures occurred over periods of many hours to days, but a key calculation is the slope of the relationship between FEV_1 and O_3 concentrations measured during the previous hour, without consideration of the background levels. The average slope from recent camp studies quoted was -0.50 ml/ppb O_3, within a concentration range of 0.01-0.16 ppm. This corresponds to a decrease in FEV_1 of 60 ml at 0.12 ppm from a base level of 2000-2500 ml, or roughly a 2.4 - 3.0% decrease in FEV_1. Other studies are comparable, although the confounding by seasonal factors, activity levels, and time spent indoors make the establishment of dose-response relationships under ordinary living conditions highly problematic.

A second indication of dose-response derives from studies of asthma. Because asthma is so common, a small increase in the risk of an episode of asthma for an individual would add up to a substantial additional national burden of illness. Depending on the baseline probability of an asthma attack, the individual risk of an attack with an increase in ozone concentration of 0.04 ppm could rise by as much as 25% (Holguin 1985) The applicability of this figure for calculations of risk assessment must be kept in perspective: it should be emphasised that the effects among persons with well characterised asthma were highly dependent on the baseline probability of an attack, so

extrapolation of these North American data to Australia tentative has been tentative (Guest et al, 1994).

A third indicator that may be useful under Australian conditions is the number of hospital admissions per ambient ozone level per person. Considering all respiratory admissions from five centres in Canada and New York State, the size of the effect ranged from 1.4 to 3.1 admissions/100 ppb O_3/day/10^6 persons (US EPA 1996a, 1996b; Burnett et al 1994). Other categorical end-points (lower respiratory symptoms, cough and chest pain on deep inspiration (dichotomised in each case to moderate or severe, in response to one or eight hours of exposure, at moderate or heavy exertion) are detailed in the recent US EPA Staff assessment (US EPA 1996).

Threshold

In general, epidemiological studies have not demonstrated an exposure threshold below which respiratory function remains intact (Table 1 in this Appendix). This is partly because of the difficulty of detecting health effects at low levels, approaching "background". One recent study of hospital admissions for respiratory disease in London suggested a threshold of about 40 to 60 ppb O_3 (maximum 1 hour or maximum 8 hour). (Ponce de Leon 1996): this may simply represent the lowest level at which any effect can be detected.

Another consideration relevant to the possibility of an adverse effect threshold is the repetition of exposure. It is possible that health effects could accumulate, given a threshold of a certain minimum number of exposure episodes. For example, the US EPA (1996b, p 72) have considered that the "nuisance" of "moderate" health effects (cough, in association with an exposure to O_3 at a level of the US one-hour standard of 012 ppm) occurring once per year, may rise to the level of an ongoing public health concern if these effects were experienced repeatedly. Whilst a single, acute O_3-induced health effect (cough or discomfort on exercise) may not - in isolation - be considered "adverse", it remains possible that a series of such episodes "could well set the stage for serious illness". "The degree of adversity of repeated "moderate" responses in healthy individuals is likely to increase with the increasing number of occurrences and with the combination of different responses" (US EPA 1996b p. 72).

The accumulated adverse effects of occasional recurrent exposures should be considered separately from the adaptation to ozone. Adaptation has been noted with repeated daily exposures (Bromberg & Koren, 1995). It has been noted that restitution of lung function and inflammatory responses occur usually within one week of an acute exposure. This observation does not, however, rule out the possibility of accumulated effects given repeated intermittent exposures to O_3. More recent, but as yet unpublished studies by Brauer et al (Bates 1997 - personal communication) would suggest that in farm workers previously exposed over a summer growing season in the Fraser Valley, BC (Brauer et al 1996), full functional recovery had occurred over the following winter period,

but that follow up over the succeeding summer growing season had shown similar decrements in lung function, again with exposure to low levels of O_3 (mean daily maximum 0.04 ppm).

Concentration range that would provide protection from the lowest observable adverse effects on susceptible populations:

In the early 1970's, the US EPA promulgated an ozone standard of 0.08 ppm (one-hour average) (Nazar 1990), a level considered unattainable during the 1970s. The US standard was relaxed to 0.12 ppm in 1979, but the accumulation of evidence since that time (Table 1 of the Appendix) clearly shows inadequate protection of health and the environment with standards set at that higher level. Based on available health effects data, together with the consideration of intersectional effects, Guest et al (1994) proposed the level of 0.08 ppm averaged over one hour as a suitable air quality goal in Australia for adoption by the NHMRC. A four-hour goal of 0.06 ppm was also proposed, because the health effects of ozone may accumulate over several hours. A contemporaneous review in the United Kingdom produced a similar recommendation, an eight-hour-average goal of 0.05 ppm (DoE,1994).

At the 119th meeting of the NHMRC, 7-8 June 1995, the Council revised the air quality goal for ozone as follows: One-hour average: 210 micrograms/cubic metre (0.10 ppm); four-hour average: 170 micrograms/cubic metre (0.08 ppm), both expressed at 0°C and 101.35kPa. The Council recommended review of these new goals within five years. This 1995 decision by the NHMRC represented a compromise between protection of human health, and environmental and other policy considerations. Similarly, the choice of a more stringent level now would require a value judgement about the level at which physiological responses come to be considered "adverse" health effects, and the persisting uncertainties associated with the incidence of adverse effects, and the range of susceptibility in the population. It is clear, by contrast, that a less stringent goal than that set by the NHMRC in 1995 would be unacceptable.

Averaging time

The averaging time has been discussed extensively by the US EPA (1996c). An eight-hour averaging time is considered physiologically most appropriate in view of the time course of ozone peaks during daylight hours, with the specified range for consideration of 0.07-0.09 ppm. These levels are less stringent than those now in place in Australia, and it is already clear from the experience in British Columbia that measurable adverse health effects can be determined in otherwise healthy outdoor workers at these levels already.

The differences between the USA and Australian approaches may reflect the perceived difficulty of the achievement of more stringent levels, together with the legal sanctions that may follow exceedances of what are standards rather than guidelines, in the USA.. An 8-hour averaging time was also chosen the United Kingdom, but 50 ppb (0.05 ppm) was the level set (DoE 1994, DoE 1996). The latter was described as an ambitious standard "which will need international action to be achieved." This level (0.05 ppm, 8-hour average) remains the longer term standard in Victoria, established in 1981 as part of that state's SEPP, and no change was recommended by Streeton (1990) following a detailed review of the then available.

DETAILED LITERATURE REVIEW [#]

The following review summarises the literature from 1993 to the present. The units used are those which were used in the original literature.

Mortality

Daily average O_3 levels have been found to be associated with daily mortality in Philadelphia County for the period 1973 to 1990 (Li and Roth, 1995). The mean 24 hour O_3 level during the study period was 19.77 ppb with a 95th percentile value of 46.8 ppb. When SO_2 and TSP were included in the model the association for O_3 was the strongest.

Moolgavkar et al., (1995) have shown that daily average levels of O_3 during the summer months for the period 1973 to 1983 were associated with daily mortality in Philadelphia. The mean 24 hour O_3 level for this period was 22.4 ppb with highest levels observed during the summer. The maximum 24-hour average level observed was 159 ppb. The association between O_3 and daily mortality persisted even when TSP and SO_2 were included in the model. The mortality risk associated with incremental changes of 100 ppb, relative to exposure on the previous day to 100 ppb O_3, was 1.15.

A study by Ito et al., (1995) has found associations between daily mortality and daily 1 hour maximum O_3 levels in both Los Angeles and Cook Counties. In both cities, O_3 showed associations up to 2 days lagged with mortality. Lags in the mortality effect have been reported elsewhere. For example, mortality due to total and cardiovascular causes and mortality in the elderly was found to be associated with maximum daily O_3 levels in Barcelona (Sunyer et al., 1996). The relative risk per 100 $\mu g/m^3$ in daily maximum O_3 level was 1.09 for both elderly and cardiovascular mortality. The median maximum daily O_3 level during the study period was 55.2 $\mu g/m^3$ with levels ranging between 7 and 189.2 $\mu g/m^3$. The strongest association was found for a 5 day lag period.

Morgan et al., (1996) have recently completed a review of possible mortality effects in Sydney as part of the 'HARP' Project, a NSW Government initiative to examine a number of the potential impacts motor vehicle emissions on the health and living environment of Sydney and the Hunter and Illawarra regions. In June 1996, a conference was held in Sydney to present the results, and to provide a platform from which to launch various strategies being developed by

the NSW Government to counteract the now recognised adverse impacts. At the HARP Conference, Morgan et al presented data derived from their review of the possible impacts that air pollution might have had on mortality patterns in Sydney over the years 1989 to 1993. Their data has since been developed further , and although not yet formally published, has been made available for the purposes of this review (Morgan et al 1996, personal communication). They undertook a time series analysis of counts of daily mortality, in conjunction with the measurements of the major pollutants in the Sydney environment (O_3, fine particulates, and Nitrogen Dioxide[NO_2]) with adjustments for seasonal and cyclical factors.

Morgan et al examined the effects on mortality patterns of an increase in pollutant levels from the 10th centile of mean daily concentrations to the 90th centile of those concentrations. They found that there were measurable mortality impacts from air pollutants in Sydney which appeared to be resulting from each of the above pollutants both individually as well as in combination. Increments in O_3 were shown to produce a 2.04% (95% CI: 0.37 - 3.73) increase in 'all causes' mortality, and a 2.52% (95% CI: -0.25 - 5.38) increase in mortality from cardiovascular causes. Particulates, on the other hand , produced a 2.6% increase in 'all causes' mortality, and 2.7% increase in cardiovascular mortality. NO_2 exposure resulted in a 7.7% increase in deaths from respiratory causes. Multiple pollutant models suggested that the effects of O_3 and particulates on 'all cause' and cardiovascular mortality, and that these effects were independent of the effects of other pollutants.

In a report just recently to hand, Loomis et al (1996) describe the results of a mortality study undertaken in Mexico City from 1990 through to the end of 1992 to assess the acute, irreversible effects of air pollution in a large population, with particular emphasis on ozone exposure. Small, but statistically significant increases in mortality were observed, relating to pollution on either the same day, or the previous day. When a single pollutant model was used, "crude" rate ratio for total mortality associated with an increase of 100 ppb in the one-hour maximum ozone concentration was 1.029 (95% CI: 1.015 - 1.044). Using a moving average showed a stronger association (rate ratio[RR] = 1.048 [95% CI: 1.025 - 1.070]), and excess mortality (defined as an increase in the number of deaths relative to the number on low pollution days) was more evident in persons over 65 years of age. Other pollutants were also related to mortality, including sulfur dioxide (RR = 1.075 [95% CI: 0.984 - 1.062]) per 100 ppb increase, and TSP (RR= 1.049 [95% CI: 1.030 - 1.067]) per 100 $\mu g/m^3$ increase when all were considered separately. When all the pollutants were considered simultaneously, then only TSP remains associated with mortality, with an excess mortality of 5% per 100 $\mu g/m^3$ increase (RR = 1.052 [95% CI: 1.034 - 1.072]), a level comparable to that seen in other cities in USA and Europe. The study provided some evidence that ozone is associated with all-cause mortality, and with mortality amongst the elderly after controlling for long-term cycles, but had little or no effect on mortality rates when other air pollutants were examined simultaneously.

Comment

There appears to be a small influence of ozone on mortality, which differs according to age group, cause of death and season. Recent community studies in Sydney suggest that overseas patterns of mortality events can be readily reproduced in Australian cities with currently prevailing O_3 levels.

Hospital Admissions and Emergency Room Visits

Significant associations between ambient levels of ozone and emergency room visits for asthma have been found for children under 5 years in Mexico City during 1990 (Romieu et al, 1995). An increase in 50 ppb in the 1 hour maximum O_3 level gave rise to a 43% increase in the number of emergency room visits on the following day. Exposure to high O_3 levels ie., > 100 ppb, for two consecutive days preceding, increased emergency room visits by 133%. The dose-response between ozone and emergency room visits for asthma was linear. Daily 1 hour maximum ozone levels during the study period ranged from 10 to 250 ppb, with a mean of 90 ppb.

Hospital admissions for respiratory disease in the elderly have been associated with daily maximum O_3 levels in Cleveland, Ohio (Schwartz et al, 1996). However, a study from the Netherlands has shown conflicting results (Schouten et al, 1996). Hospital admissions for the elderly for respiratory causes were found to be significantly associated with 8 hour maximum and 1 hour maximum O_3 levels in Rotterdam but were not statistically significant in Amsterdam. The mean 8 hour O_3 values were 86 and 82 µg/m³ in Amsterdam and Rotterdam respectively: the maximum 8 hour O_3 levels were 252 and 286 µg/m³. The mean 1 hour O_3 levels were 97 and 96 µg/m³. The relative risk for a 100 µg/m³ increase in mean 8 hour O_3 level were 1.127 in Amsterdam and 1.344 in Rotterdam.

Ozone levels in London have been associated with hospital admissions for respiratory disease in the 15 to 64 years and above 65 years age groups (Ponce de Leon, 1996). The relative risks of admission per 29 ppb increase in 8 hour O_3 level (10th to 90th percentile) were 1.05, 1.08, and 1.06 for all ages, 15 to 64 years and above 65 years age groups respectively. This association was observed for a 1 day lag period and was stronger in the warmer months. There was evidence of a threshold at about 40 to 60 ppb O_3 (maximum 1 hour or maximum 8 hour). Mean maximum 1 hour and maximum 8 hour O_3 levels during the study period were 20.6 and 15.6 ppb with 95th percentile values of 46 and 37 ppb respectively.

Emergency room visits for asthma in central New Jersey have been positively associated with O_3 levels during the summer months for the period 1986-1990 (Weisel et al., 1995). A 28% increase in emergency room visits was observed when O_3 levels were greater than 0.06 ppm compared to periods when levels

were lower than 0.06 ppm. Mean O_3 levels during the study period ranged from 0.053 and 0.057 ppm. The results indicate that an increase of between 0.3 and 0.8 emergency visits per day in this study population for asthma is associated with each 0.01 ppm increase in ozone level.

An earlier study also found a statistically significant association, after controlling for temperature, between ozone exposure and asthma emergency room visits in New Jersey for the period May 1988 to August 1989 (Cody et al., 1992). This association was observed for the current and previous day exposures. Mean 24 hour O_3 levels during the study period were 0.048 ppm.

Strong associations have been found for hospital admissions for respiratory causes and ozone levels in New York City and Buffalo, New York, during the summer (Thurston et al ., 1992). Both total respiratory and asthma admissions were associated with ozone levels on the current and following days. In Buffalo relative risks of admission for respiratory causes and asthma on high pollution days compared to the mean, were 1.22 and 1.29 respectively. Similar calculations for New York City yielded relative risks of 1.19 for total respiratory and 1.23 for asthma. The results show that although New York City had higher pollution levels than Buffalo, the effect on hospital admissions was greater. This was thought to be due in part to higher acidity in Buffalo. The health effects of exposure to ozone are thought to be potentiated by H^+. Mean 1 hour daily maximum O_3 levels during the study period were 61 ppb and 70 ppb in New York and Buffalo respectively, with maximum levels 158.5 ppb and 146 ppb respectively.

A study from Atlanta (White et al., 1994) has found an association between emergency room visits for asthma for children aged 1 to 16 years and elevated levels of ozone. The average number of visits for asthma or reactive airway disease was 37% higher on days following periods with maximum O_3 levels in excess of 0.11 ppm.

A statistically significant association has been found between 8-hour maximum O_3 levels and hospital admissions for respiratory illness with a 4 day lag in Montreal during the summer months (Delfino et al., 1994). The mean maximum 8 hour O_3 level during the study period (1984-1988) was 59.7 µg/m³ with a 90th percentile value of 100.9 µg/m³.

Ozone levels in Minneapolis-St. Paul have been associated with hospital admissions for pneumonia in the elderly (Schwartz, 1994). The relative risk for a 50 ppb increase in daily O_3 level was 1.15. The mean 24 hour O_3 level for the study period was 26 ppb with a 90th percentile value of 58 ppb. The strongest association was observed for a 1 day lag. A similar study in Detroit (Schwartz, 1994) found similar results with a relative risk of 1.026 for a 5 ppb increase in daily average O_3 level (1.26 per 50 ppb). Associations were also observed for hospital admissions for COPD and daily O_3 level with a relative risk of 1.028 per 5 ppb increase (1.28 per 50 ppb). No association was observed for asthma

admissions. These results were observed in the elderly. The mean 24 hour O_3 level during the study period was 20 ppb.

A study conducted at the Royal Children's Hospital in Melbourne found no association between O_3 levels and attendances at the Emergency Department for asthma (Rennick and Jarman, 1992). Ozone days were defined as days with a one-hour ozone value of ≥ 0.09 ppm, not a very sensitive measure of exposure. All smog variables explained only 2.3% of the variance in asthma attendance, but a relationship was found between days when the airborne particulate index was above threshold and asthma admissions.

Ozone was found to be associated with hospital admissions for respiratory illness in Ontario, Canada, during the summer months (Burnett et al, 1995). In contrast, O_3 was not associated with hospital admissions for cardiac diseases. The mean daily 1 hour maximum O_3 level during the study period (1983-1988) was 36.3 ppb.

A study from Birmingham, Alabama, (Schwartz, 1994c) has shown that 24 hour O_3 levels are associated with hospital admissions for pneumonia with a 2-day lag, and COPD with a 1-day lag. The relative risks per 50 ppb increase in O_3 level were 1.14 and 1.17 for pneumonia and COPD respectively. Use of peak O_3 levels did not change the relationship and the relationship existed only during the summer months. The mean 24 hour average O_3 level during the study period was 25 ppb with a 90th percentile value of 37 ppb.

A community study undertaken in Melbourne in recent years, as yet unpublished except as an abstract (Abramson et al 1994), and as a methodological report (Goldsmith et al 1996), looked at the relationships, using spectral and state-space analysis, between air pollution, meteorological conditions, air borne pollens and asthma admissions. Abramson et al found that their model explained 23% of the observed variation in daily asthma admissions to the various Melbourne teaching hospitals involved in the study, of which 13.2% could be attributed to ozone effects, whereas only 1.0% could be attributed to particulates (nephelometry), and 0.8% to NO_2.

As part of the HARP studies already referred to in Sydney, time series analyses for the years 1990 - 1994 of counts of daily hospital admissions for asthma, chronic obstructive lung disease, and heart disease with levels of major pollutants (O_3, NO_2, and particulates) have been undertaken and recently reported verbally, although not as yet formally published (Morgan et al 1996b). Again the effects of increasing pollutant levels from the 10th centile to the 90th centile were assessed. In this analysis, Morgan et al found that increases in O3 as described resulted in a 2.5% (95% CI: -0.35-5.44) increase in admissions for heart diseases, with the strongest effect in the elderly. In comparison, particulate increase resulted in a 2.8% increase in heart disease admissions, and increasing NO2 resulted in a 7.2% increase in cardiac admissions.

Comment

The strongest effect on admissions is usually observed on a day subsequent to the high level of ozone exposure. These studies do not give any indication of a safe threshold level of exposure to ozone. The elderly appear to be especially susceptible to the effects of ozone resulting in increased admissions for cardiac conditions.

Asthma and Respiratory Symptoms

A study of German school children has shown that an increase in ambient O_3 levels initiates a reversible inflammatory response of the upper airways in normal children (Frischer et al., 1993). Nasal lavages were performed following high ($\geq 180 \, \mu g/m^3$) and low ($\leq 140 \, \mu g/m^3$) O_3 days and the fluids analysed for polymorphonuclear leucocytes (PMN) and a number of biochemical markers such as albumin, tryptase, eosinophil cationic protein (ECP) and myeloperoxidase. Linear regression analysis of $\log_{10}$ PMN counts yielded a significant effect for ozone. A significant increase was observed for ECP and myeloperoxidase on high O_3 days.

In a study by Ostro et al., (1993) significant associations between upper and lower respiratory tract symptoms with O_3 were found for non smoking adults in Southern California. Mean O_3 levels during the study period, September 1978 to March 1979, were 1 hour max: 9.86 pphm; 7 hour: 6.74 pphm with maximum values of 1hour: 43 pphm; and 7 hour: 27.71 pphm. The odds ratio for lower respiratory tract symptoms and 1hour daily maximum O_3 levels was 1.22 per 10 pphm increase in O_3, and 7 hour O_3 the odds ratio was 1.32 per 10 pphm increase. The observed effects were greater among individuals with a pre-existing respiratory infection. With regard to upper respiratory symptoms, only the 7 hour average measurement of O_3 was statistically significant with an odds ratio of 1.09. A statistically significant association was also found between O_3 measures and the probability of reporting eye irritation.

Comment

The possibility that ozone may initiate asthma remains controversial, but it does clearly exacerbate this condition. Persons with asthma constitute therefore a particularly susceptible sub-population, with evidence of significant enhancement of response if previously exposed to another pollutant.

Lung Function and Airways Responsiveness

Studies of school children in Mexico City have investigated the effects of O_3 on lung function and respiratory symptoms (Castillejos et al., 1992 & 1995). In the earlier study the mean ozone level prior to spirometry testing was found to be associated with a decrement in FVC but not FEV_1 or FEF_{25-75}. In contrast, the mean O_3 level during the previous 24, 48 and 168 hour were associated with significant decrements in FEV_1 and FEF_{25-75} but not FVC. These decrements in FEV_1 and FEF_{25-75} may reflect an inflammatory process in the airways that differs from the acute physiological response to O_3 associated with a decrement in FVC and the inability to take a deep breath (Castillejos et al., 1992). Children with chronic phlegm showed a consistently greater decrement in lung function indicating that these children may be more susceptible to respiratory irritants. In the latter study (Castillejos et al., 1995) for children aged between 7.5 and 11 years of age, decrements in lung function were observed on exposure to O_3 levels greater than 150 ppb for 1 hour while exercising. These decrements were statistically significant only in the fifth quintile, ie., 182-365 ppb.

A study from the UK has found an association between ambient O_3 levels and bronchodilator use, dyspnoea, eye irritation and peak expiratory flow readings in patients with COPD (Higgins et al., 1995). During the study period the maximum 24 hour level of O_3 was 55 $\mu g/m^3$ and the maximum 8 hourly level was 71 $\mu g/m^3$. In hyperreactive patients, O_3 levels were also associated with wheeze.

Just recently published is a study from British Columbia (Brauer et al 1996) which details the results of field studies under taken in the Fraser Valley over the 1993 summer season. Farm workers in the outdoors all day for between 8 and 14 hours, exposed to mean daily ambient maximum 1 hour ozone concentrations of 40 ppb (range 13 to 84 ppb), with very low levels of exposure to confounders such as fine particulates and acid aerosols, had serial measurement of simple lung function (FVC, $FEV_{1.0}$) morning and evening for the summer working season. 47 out of 53 workers had negative slopes when evening lung function parameters were correlated with the maximum daily ozone concentration. these associations were still apparent the following morning, and Brauer et al concluded that exposure of these otherwise healthy outdoor farm workers to ambient ozone concentrations below 85 ppb was associated with decreased lung function over the working day, and that this effect persisted until the following day.

Subsequent follow-up studies, as yet unpublished, undertaken the following summer season in the same group of farm workers would suggest that lung function returned to pre-exposure levels over the intervening winter, and that further exposure to summer-time ozone the next year produced the same pattern of response (Bates 1997, personal communication). Whether or not there is long-term irreversible damage remains to be determined.

Comment

These studies confirm responses to O_3 that have been identified by pulmonary function tests over the past decade, and now show a new low level of exposure (<85 ppb) at which sensitivity is detected.

Laboratory Studies

Controlled Human Exposures

Folinsbee et al., (1994) have shown that exposure with intermittent exercise to 0.12 ppm O_3 for 6.6 hours on 5 consecutive days, causes decreases in lung function and an increase in respiratory symptoms in healthy adults. These responses are most pronounced on the first day and nonsignificant by the third and subsequent days. The percentage change in FEV_1 after O_3 exposure averaged -13% on the first day to +0.18% on the fifth day. In addition, airway responsiveness was significantly increased after each O_3 exposure. Symptoms of cough and pain on deep inspiration increased significantly on day 1 only.

Exposure of healthy and asthmatic adults to 0.2 ppm O_3 intermittently for 6 hours has shown significant increases in IL-8 and IL-6 levels as well as polymorphonuclear neutrophils in the asthmatic subjects (Basha et al, 1994). No differences were observed in pulmonary function, ie., FEV_1, FVC, FEV_1/FVC and sRaw, between the asthmatic and normal groups. The authors conclude that asthmatic subjects exposed to O_3 develop a greater BALF neutrophilia than normal subjects, though without acute symptoms or changes in pulmonary function. Further, the elevated levels of IL-8 in the lavage fluid of O_3-exposed asthmatics suggest an important role for this neutrophil chemotactic and activating factor.

Short-term exposure to 0.2 ppm O_3 has been shown to cause bronchial tissue injury in addition to inflammatory response in the distal lung (Aris et al., 1993). In this study 14 healthy, athletic subjects were exposed to either 0.2 ppm O_3 or clean air for 4 hours during moderate exercise. Eighteen hours after exposure isolated lavage of the left bronchus and forceps biopsy of the bronchial mucosa were performed. The mean total cell count and lactate dehydrogenase (LDH) concentration in the isolated airway lavage was significantly greater after O_3 exposure. Morphometry showed that O_3 exposure caused an acute inflammatory cell influx into the airway. In addition there were statistically significant decreases in FEV_1 and FVC for the O_3 exposed group, and a statistically significant increase in sRaw. The O_3 exposures resulted in a significantly larger increase in mean respiratory rate and larger mean decrease in tidal volume. Proximal airway lavage data showed increases in total cell counts, neutrophils and epithelial cells, and LDH and IL-8 concentrations. The bronchial biopsy specimens were noted to show an O_3-induced neutrophil influx into bronchial tissue. These results were confirmed by morphometry. No significant differences were observed in eosinophil counts between O_3 and air exposures. No association was observed between spirometric responses and

BAL inflammatory end points after exposure to O_3. These results suggest that spirometric responses do not predict O_3-induced inflammatory changes.

A study by Koenig et al (1990) has shown that exposure to 120 ppb O_3 for 45 minutes with intermittent exercise increases the subsequent response to SO_2 (15 minute exposure at 120 ppb). Exposure to air-SO_2 and O_3-O_3 did not cause significant changes in pulmonary function. Pulmonary function measurements assessed were FEV_1, total respiratory resistance R_T and maximal flow ($Vmax_{50}$). Exposure to 100 ppb SO_2 after exposure to O_3 caused an 8% decrease in FEV_1, a significant increase in R_T (19%) and a 15% decrease in $Vmax_{50}$. These authors concluded that prior exposure to O_3 increased bronchial hyper-responsiveness in these subjects such that they responded to an ordinarily subthreshold concentration of SO_2.

A study by Hatch et al., (1994) has compared the dose and effect of O_3 in rats and humans. The results of this study indicated that exercising humans had four to five times the ^{18}O concentrations in all of their BAL constituents than rats. Humans also had significant increases in all of the effects markers after 0.4 ppm O_3 where rats did not. Rats that were exposed to higher concentrations of $^{18}O_3$ (2 ppm) had levels of ^{18}O in BAL that were more comparable to but lower than those of exercising humans. The authors conclude that O_3 toxicity in resting rats underestimates effects in exercising humans because rats have a lower than expected dose of O_3 to the distal lung. This finding needs to be considered when extrapolating toxicity data from rats to humans.

Ozone has been found to increase bronchial allergen responsiveness in subjects with mild allergic asthma or rhinitis (Jorres et al., 1996). Twenty four subjects with mild, stable asthma, 12 subjects with allergic rhinitis without asthma and 10 healthy subjects were exposed to 250 ppb O_3 or filtered air for 3 hours with intermittent exercise. Airway responsiveness to methacholine was determined 1 hour before and 1 hour after exposure, and allergen responsiveness 3 hours after exposure. In subjects with asthma FEV_1 decreased by 12.5%, and in subjects with allergic rhinitis mean FEV_1 decreased by 7.8% after exposure to O_3 and 1.3% after exposure to filtered air. The severity of symptoms associated with exposures was recorded in a written questionnaire. The panel of symptoms comprised nose and throat irritation, cough, chest tightness, shortness of breath, headache, nausea, thirst and dizziness. Symptoms of upper respiratory tract, lower respiratory tract and general symptoms were also assessed.

Hiltermann et al., (1995) have shown that exposure to ozone at 0.4 ppm for 2 hours with alternating periods of 15 minute rest and exercise causes a transient increase in the maximal degree of airway narrowing to methacholine in both asthmatic and non-asthmatic subjects. All subjects experienced shortness of breath and cough shortly after O_3 exposure. Directly after O_3 exposure the FEV_1

dropped 15.3% in the non-asthmatic subjects and 15.2% in asthmatic subjects compared with pre-exposure values. The symptoms and the fall in FEV_1 were reversible. The effect of ozone on the dose-response curve to methacholine was significantly larger for the non-asthmatic than for the asthmatic subjects. In both non-asthmatic and asthmatic subjects the percentage of neutrophils in sputum was significantly higher 12 hours after O_3 exposure compared with air exposure.

The effect of pre-exposure to O_3 on exercise-induced asthma has been investigated (Fernandes et al., 1994). Exposure to 0.122 ppm O_3 for 1 hour on each of 3 days 1 week apart followed by an exercise challenge has shown no significant difference in maximal percentage fall in FEV_1 or V_{40p} compared to pre-exposure to air. The authors conclude that their data indicate that previous exposure at rest to a concentration of O_3 that has been previously shown to augment the broncho-constrictor response to allergens did not increase the bronchoconstriction response to subsequent exercise nor did it change the time course of such bronchoconstriction. Similar results have been found in a study by Weymer et al., (1994). In this study pre-exposure to 0.1, 0.25 or 0.4 ppm O_3 for 1 hour with intermittent light exercise does not enhance or induce exercise induced asthma as measured by spirometry after a standardised near-maximal exercise challenge conducted 1 hour after cessation of O_3 exposure. A decrease in FEV_1 was seen immediately after the 1 hour exposure to 0.4 ppm O_3, but spontaneous reversal was nearly complete during the subsequent 1 hour rest period in clean air. A typical response to O_3, chest soreness, chest tightness and total lower respiratory symptoms, coincided with this acute reduction in FEV_1.

The inflammatory effects of O_3 in the upper airways have been investigated by McBride et al., (1994). Ten asthmatic and eight non-asthmatic subjects were exposed to clean air, 120 ppb O_3 or 240 ppb O_3 for 90 minutes during intermittent exercise. Pulmonary function tests, posterior rhinomanometry, and nasal lavage were performed before and after exposure. Leucocyte counts, and chemotactic factors leukotriene $B_4(LTB_4)$, platelet activating factor (PAF), and interleukin-8 (IL-8) were analysed from nasal lavage fluid. A significant increase in the number of white blood cells in lavage fluid of asthmatic subjects was detected both immediately and 24 hours after exposure to 240 ppb O_3 as was a significant increase in epithelial cells immediately after exposure. No significant cellular changes were seen in non-asthmatic subjects. No significant changes in pulmonary or nasal function or biochemical mediators were found in either the asthmatic or non-asthmatic subjects. These authors conclude that short-term exposure to an ambient concentration of O_3 induces upper airway inflammation in subjects with asthma. A significant increase was observed in the number of neutrophils and epithelial cells recovered in the nasal lavage fluid of these subjects 7 to 10 minutes after exposure to 240 ppb O_3 and neutrophil levels were also significantly higher 24 hours after O_3 exposure. In contrast, these inflammatory changes were not observed after exposure to air or 120 ppb O_3 or in non-asthmatic subjects after either O_3 exposure.

A study by Frampton et al., (1995) has investigated the responses of both healthy and asthmatic humans to sequential exposure to sulphuric acid aerosol and O_3. Subjects were exposed for 3 hour to 100 $\mu g/m^3$ sulphuric acid and saline (as a control) aerosols followed 24 hours later by 3 hour exposures to O_3 (0.08, 0.12, or 0.18 ppm). Each subject was studied 4 times. For the healthy group, no convincing symptomatic or physiological effects of exposure to either the aerosol or O_3 on lung function were found. For the asthmatic group, pre-exposure to sulphuric acid altered the pattern of response to O_3 in comparison with saline pre-exposure and appeared to enhance the small mean decrements in FVC that occurred in response to 0.18 ppm O_3. Individual responses among asthmatics were quite variable.

The effects of 0.4 ppm O_3 on nasal inflammatory responses in asthmatics has been studied by Peden et al., (1995). Exposure to O_3 led to an increase in allergic response in these asthmatic subjects. Less allergen was required to induce nasal symptoms after exposure to O_3 exposure, indicating a possible effect on the immediate-phase response to allergen. Ozone exposure also had an intrinsic effect on the influx of both eosinophils and PMN into the nasal airway, which was independent of the allergen challenge. ECP levels were also augmented by exposure to O_3. These results suggest that eosinophils may be activated by O_3 and that ECP may be used as a surrogate marker for eosinophil influx.

Comment

These studies provide further information on inflammatory and cellular responses. Interspecies differences are noted. The studies demonstrate the lack of sensitivity of spirometry and other tests of pulmonary function to effects of O_3 on the lung.

Animal Studies

Exposure to 3 ppm O_3 for 2 hours each day for 3 days has been shown to increase airway responsiveness to acetylcholine (Ach) in dogs both sensitive and insensitive to *Ascaris suum* antigen (AA) (Yanai et al., 1990). A decrease in Ach provocation concentration from 0.541 to 0.102 mg/ml was observed after exposure to O_3. Ozone also increased airway responsiveness to AA in AA sensitive dogs and decreased the provocation dose of AA by approximately a factor of 5. The O_3 induced hyper-responsiveness to Ach returned to baseline levels within 2 weeks, but hyper-responsiveness to AA continued for a period greater than 2 weeks. The plasma histamine concentration after AA challenge was significantly higher after O_3 exposure than before. OKY-046, an inhibitor of thromboxane synthesis, inhibited the O_3 induced increase in responsiveness to Ach, but had no effect on the O_3 induced increase in responsiveness to AA and the increase in plasma histamine concentration. The authors conclude that the

results of this study suggest that O_3 increases susceptibility to antigen in sensitised dogs via a different mechanism from that of O_3 induced muscarinic hyper-responsiveness. The mechanism for the latter response may involve inhibition of thromboxane generation.

In a study by Sumimoto et al (1990) guinea pigs were exposed to either 1,3 or 5 ppm O_3 before sensitisation with ovalbumin or before provocation with the same. This protocol was to test two possible mechanisms for the enhancement of asthma attacks. Exposure to O_3 prior to sensitisation increased IgG1 antibody and the incidence of bronchial anaphylaxis only at a concentration of 5 ppm. The effect of exposure to O_3 before provocation was more significant with a marked enhancement in the induction of bronchial anaphylaxis at each of the O_3 concentrations, 1,3 and 5 ppm. The provocation threshold to ovalbumin was decreased from 0.5 to 0.02% and this enhancement appeared to depend on airway hyper-responsiveness.

The role of superoxide anions in O_3 induced airway hyper-responsiveness has been examined using Brown Norway rats in a study by Tsukagoshi et al., (1995). The results of this study show that airway responsiveness to inhaled acetylcholine and bradykinin is significantly increased 18-24 hours after O_3 exposure for 3 and 6 hours at 3 ppm and that airway hyper-responsiveness to bradykinin only occurs after 6 hours of O_3 exposure. This was associated with an increase in neutrophil counts in bronchoalveolar lavage fluid (BALF). Apocynin, an inhibitor of superoxide anion-generating NADPH oxidase, inhibited the increase in airway hyper-responsiveness to bradykinin but not to acetylcholine without affecting the neutrophil counts in BALF. The antioxidants allopurinol and deferoximine prevented O_3 induced airway to both acetylcholine and bradykinin but did not reduce neutrophil counts. The authors conclude that superoxide anions released from inflammatory cells in the airway may be involved in ozone induced airway hyper-responsiveness.

A study by Petruzzi et al. (1995) has shown that continuous exposure of mice to O_3 at levels ranging between 0.2 to 0.6 ppm from 6 days prior to mating to day 17 of pregnancy had no significant effects on either reproductive performance, postnatal somatic and neurobehavioural development or adult motor activity. Some of the results pointed to subtle or borderline behavioural deficits.

There is a growing body of evidence that indicates that rodents and humans can develop a tolerance to repeated O_3 exposures and that the nature and intensity of the toxicity may change as the length of exposure increases. In a study by Watkinson et al., (1995), male Fischer 344 rats were exposed to O_3 at 0.5 ppm for either 6 or 24 hours/day for a 5 day period followed by a recovery period of 7 days. The results showed that the toxicity of O_3, as monitored by bronchoalveolar lavage, increased in magnitude and duration of O_3 exposure and with ambient temperature. Exposure to O_3 at ambient temperatures of 22 and 10^0C produced significant decreases in heart rate and body weight. These effects were not observed after exposure at 34^0C. Decreases in these parameters

reached their maxima over the first two days of exposure and returned to their control levels after the third day of exposure.

A study by Schlesinger et al., (1992) has examined the type and temporal progression of changes in tracheobronchial mucociliary function and structure in rabbits due to intermittent long-term exposures to O_3. Effects were found with relatively short daily exposures to O_3 at levels below 0.12 ppm. Exposure to O_3 resulted in an increase in secretory cell number by 4 months. The effects of O_3 were characterised by adaptation with continued exposure.

The cyclo-oxygenase metabolites of arachidonic acid have been shown to cause hypersecretion of mucus and, *in vitro,* to cause constriction of airway smooth muscle. In a study by Fouke et al., (1991) mongrel dogs were exposed to 0.5 ppm O_3 for 2 hours. After exposure an increase in respiratory resistance, a decrease in dynamic compliance and an increase in airway reactivity, with no changes in cyclo-oxygenase products of arachidonic acid metabolism, were observed. The authors conclude that a change in the levels of these metabolites are not prerequisites for O_3-induced changes in lung mechanics or airway reactivity.

Lew et al., (1990) have shown that N-acetyl-β-D-glucosaminidase (NAGA) activity of bronchoalveolar lavage fluid from guinea pigs exposed to O_3 is markedly elevated. Guinea pigs exposed to O_3 at 3 ppm for 2 hours showed substantial muscarinic hyper-reactivity 30 min after exposure. It was also found that NAGA activity of mixed bronchoalveolar cells in vitro, and specifically bronchoalveolar macrophages, from O_3 exposed animals was increased. This evidence suggests that these macrophages are, at least in part, a source of the increased NAGA in the airways post O_3 exposure.

In a study by El-Fawal et al., (1995), the ability of a single 3 hour inhalation exposure to O_3 and to O_3 plus H_2SO_4 to induce nonspecific airway hyper-responsiveness in healthy rabbits has been investigated. Airway responsiveness was assessed using an in vitro assay involving administration of increasing doses of acetylcholine to bronchial rings obtained from rabbits exposed to 0.1 to 0.6 ppm O_3 or to mixtures of O_3 and 50 to 125 $\mu g/m^3$ H_2SO_4. Bronchial hyper-responsiveness was observed at all O_3 concentrations, but the combination of pollutants results in antagonism. When exposed to the mixture this hyper-responsiveness was no longer evident.

Comment

Animal studies continue to provide insights into the pathogenesis of the human health effects of ozone. The effects are principally sustained in the lung. Tolerance may develop in the short term, but the long term effects are not well characterised. The antagonism between the effects of various pollutants sometimes results in a less measurable physiological change in lung function, compared with isolated exposure, but may have additional biological effects, short and long term, that have not been identified.

In Vitro Studies

Destruction of the elastin-rich lung alveoli has been long recognised as the principal pathologic finding in emphysema (Winters et al., 1994). Emphysema is also associated with the genetic deficiency of α_1-proteinase inhibitor, which protects the lung by inhibiting human neutrophil elastase, the principal elastolytic enzyme found in the body. Laboratory studies have suggested that excess proteolysis is responsible for the development of emphysema. A study by Winters et al., (1994), has indicated that O_3 may contribute to lung disease by directly damaging elastin and by increasing its susceptibility to proteolysis.

In a study by Tarkington et al., (1994) respiratory epithelial cells and tracheal explants were exposed to O_3 in vitro. Exposure of epithelial cells without culture medium caused substantial damage. The cell viability was 20%, as compared with cells without exposure. When culture medium was added on top of the epithelial cell surface, the damage caused by O_3 was reduced. The viability was about 45% of control values with 0.2 ml of culture fluid added. Electron microscopy revealed extensive cell damage following exposure to 1 ppm O_3 for 2 hour. Cell membrane fragmentation, chromatid condensation, vacuolation and encapsulation of various organelles were observed in the cells exposed to O_3. There was a good correlation between the duration of exposure and the loss of cell viability with about 60% of cells remaining viable after 2.5 hours of exposure, and only 25% of cells still viable after 15 hours of exposure. Necrotic cells were observed in the tracheal explants exposed for 24 hours to 1,2 or 3 ppm O_3. These cells included ciliated, serous, globular leucocyte or unidentified phenotypes. There was an apparent concentration dependent response to exposure to O_3, with the response to 3 ppm O_3 significantly different from the other groups.

A human bronchial epithelial cell line, BEAS-2B, which was immortalised by transformation with SV40 virus, was cultured in the presence of either 0.1 to 1 ppm O_3 (Sun et al., 1994). Decreased viability and decreased synthesis of various macromolecules was observed. The extent of cell injury was proportional to O_3 exposure. Damage included fragmentation of the cell membranes, dis-aggregation of cellular organelles, and the condensation of chromatid. Ozone was able to produce significant damage to cultured cells at levels as low as 0.1 ppm. At 1 ppm of O_3, the duration of exposure required to reduce cell viability by 50% was 4.5 hours. In addition O_3 exposure induced and/or enhanced the synthesis of a 45 kD protein. The extent of increased synthesis of this protein was related to the concentration of O_3 to which the cells were exposed. At a concentration of 0.4 ppm, the elevation was 2 fold, reaching 3 to 3.5 fold at a concentration of 1 ppm. Synthesis of the protein was detectably elevated 20 hours postexposure Actinomycin D prevented enhanced synthesis of this protein suggesting transcriptional regulation of expression of the 45 kD protein.

McKinnon et al., (1993) investigated the effects of O_3 exposure on eicosanoids released from BEAS-S6 cells. Thromboxane B_2 (TxB_2), prostaglandin E_2 (PGE_2), leukotreine C_4 (LTC_4), LTD_4, LTE_4 and 12-hydroxyheptadecatrienoic acid (HHT) were released after exposure to O_3 at concentrations of 0.1, 0.25, 0.5 and 1 ppm. These eicosanoids are released from cyclo-oxygenase and lipo-oxygenase pathways of arachidonic acid metabolism following exposure to O_3.

The effect of O_3 on the production of cytokines with depletion of reduced glutathione and haemolysis has been investigated in human blood (Bocci et al., 1993). A transient exposure (30 secs) of blood to up to 78 μg of O_3 per ml of blood does not depress the production of cytokines even though there is a slight increase in haemolysis and a small decrease in intracellular reduced glutathione. In contrast either a constant (up to 30 sec) exposure to an O_3 flux or a high O_3 concentration (108 μg/ml) markedly decreases reduced glutathione levels and depresses cytokine production. GSH levels were reduced by 5.7 and 8.3% with O_3 concentrations of 42 and 78 μg/ml. GSH levels returned to normal 30-60 min after O_3 exposure.

A study by Van der Vliet et al., (1995) has shown that prolonged exposure of human blood plasma to O_3 causes oxidative damage to plasma proteins and lipids. In addition it was observed that O_3 reacts primarily with aqueous antioxidants ascorbate and urate. Reactive absorption of O_3 by plasma ascorbate and urate was found to be more efficient at low (2 ppm) O_3 levels rather than at high (16 ppm). Addition of either GSH or DHLA, known antioxidants, did not inhibit oxidation of plasma proteins and lipids during exposure to O_3, nor did it attenuate depletion rates of ascorbate or urate. The authors suggest that these results indicate that added thiols cause increased reactive absorption of O_3, rather than preventing reaction of O_3 with other plasma constituents. An earlier study by Cross et al., (1992) found similar results. In this study exposure human blood plasma to 16 ppm O_3 for 6 hours produced rapid oxidation of uric and ascorbic acids, a slower oxidation of protein-SH groups and no loss of bilirubin or α-tocopherol. There was little formation of lipid hydroperoxides. These authors conclude that oxidative damage to lipids must not be assumed to be a key mechanism of respiratory tract O_3 toxicity, and that uric acid in the upper airway secretions may play a significant role in removing O_3.

Tosi et al., (1994), have shown that on exposure of monolayers of human tracheal epithelial cells to O_3 at 2 ppm for 30 min, or 0.5 ppm for 2 hours, the percentage of neutrophils (PMN) adhering to these cells increased from <5% to a maximum of approximately 75% by 18 to 24 hours after O_3 exposure. No change was observed within the first 2 hours after O_3 exposure, but there was a statistically significant increase in PMN adhesion by 8 hours after exposure. This increase was not associated with an increase in epithelial expression of ICAM-1.

Exposure to O_3 has been shown to increase the uptake of particles in tracheobronchial epithelial cells (Churg et al., 1996). In this study tracheal explants were exposed to either air or O_3 in varying concentrations from 0.01 to 1.0 ppm for 10 mins and subsequently to a suspension of either amosite asbestos or titanium dioxide for 1 hour. The explants were then incubated in an air/CO_2 environment for 1 week. This increase in uptake occurs with brief exposures at very low levels of O_3 and appears to be mediated by hydrogen peroxide and possibly by the hydroxyl radical. This process is a direct effect of O_3 on the tracheobronchial epithelium and occurs in an explant system that is essentially free of inflammatory cells.

Lactate dehydrogenase (LDH) release has been used as an indicator of sublethal oxidant injury to membrane integrity in both in vivo and in vitro studies. In a study by Dumler et al., (1994), the effects of O_3 exposure at 0.5 ppm for 3 hours on three types of cultured respiratory epithelial cells (primary cultures of human nasal cells and primate bronchial cells, and the A549 type II pneumocyte-derived cell line) were examined. Cells were grown to confluent monolayers and then exposed to O_3 or filtered air. LDH release was significantly increased following O_3 exposure of all cell types: a 75% increases from human nasal cells, a 79% increase from primate bronchial cells, and a 69% increase from A549 cells.

In a study by Mayer and Branscheid (1992), exposure of cultured human fibroblasts to 0.5 ppm O_3 for 20 hours resulted in a significant increase in cellular mortality by 29%; after exposure to 2.5 ppm O_3 for 4 hours, the increase was 74%. A marked difference in sensitivity to O_3 was observed between fibroblast lines from different individuals. This variability was more evident after exposure to O_3 for 20 hours at 0.5 ppm.

Exposure of human tears to O_3 at concentrations ranging between 0.03 to 0.12 ppm for periods between 5 and 30 mins has been shown to cause a marked destruction of tear proteins (Schmut et al., 1994). Lysozyme, a protein in tears which is responsible for the bactericidal activity, was found to be very susceptible to O_3 degradation with short exposures. The destruction of these proteins was dependent on both time of exposure and the concentration of O_3.

Comment

Mechanisms in addition to oxidative damage are being actively investigated. The responses to ozone are highly variable, consistent with the results of in vivo studies. The induction of emphysema remains a possible effect, but these studies do not provide information directly relevant to setting the NEPC standards.

Conclusions

Epidemiological studies have shown that O_3 levels are associated with increased hospital admissions for cardiac conditions, especially in the elderly, and increased emergency room visits for respiratory disease (including asthma) and with increases in respiratory symptoms, airway responsiveness and decreases in lung function. These effects are correlated with both daily 1 hour maximum and 8 hour maximum O_3 levels with the strongest effects observed with a 1 day lag. There is also some evidence that O_3 may be associated with an increase in daily mortality from both 'all causes', and from cardiovascular causes.

The effects on lung function and airway responsiveness have also been observed in controlled exposure studies in both human and animal studies. Results of bronchoalveolar lavage have shown that the observed response may be due to an inflammatory process. No association between spirometric responses and BAL inflammatory end points has been observed. The observed effects appear to greater on asthmatics than on healthy subjects. Ozone has also been found to increase bronchial allergen responsiveness in sensitive groups.

TABLE 2
Summary of Adverse Health Effects of Ozone

Sensitive Subpopulations

Epidemiological Studies

HEALTH ENDPOINT	STUDY POPULATION	LOWEST LEVEL AND AVERAGING TIME	UPPER LEVEL AND AVERAGING TIME
Mortality	General	19.77 ppb mean 24hour	159 ppb mean 24 hour
	Elderly	3.5 ppb mean maximum 24 hour	94.6 ppb mean maximum 24 hour
	Individuals with cardiovascular disease	3.5 ppb mean maximum 24 hour	94.6 ppb mean maximum 24 hour
	Sydney, 1989 - 93	10th centile	90th centile
Hospital Admissions	Children < 5 years	10 ppb daily 1 hour maximum	250 ppb daily 1 hour maximum
	Individuals with Respiratory Disease	20.6 ppb mean max 1 hour 15.6 ppb mean max 8 hour Threshold observed at 40 to 60 ppb max 1hour or max 8 hour	158.5 ppb max 1 hour 59.7 ppb mean max 8 hour
	Asthmatics	48 ppb mean 24 hour	110 ppb mean 24 hour
	Elderly with Pneumonia	20 ppb mean 24 hour	
	Individuals with COPD	20 ppb mean 24 hour	
	Sydney, 1990 - 94	10th centile	90th centile
Respiratory Symptoms	Children	<70 ppb mean 24 hour	>90 ppb mean 24 hour
	General	98.6 ppb mean max 1 hour 67.4 ppb mean max 7 hour	430 ppb max 1 hour 277 ppb max 7 hour
Lung Function	Children	182 ppb 1 hour	365 ppb 1 hour
	Individuals with COPD		27.5 ppb mean 24 hour 35.5 ppb max 8 hour

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Controlled Exposure Studies

HEALTH ENDPOINT	STUDY POPULATION	LOWEST LEVEL AND AVERAGING TIME	UPPER LEVEL AND AVERAGING TIME
Lung Function	Healthy Subjects	0.12 ppm 6.6 hours	0.4 ppm 2 hours
	Asthmatics	0.4 ppm 1 hour	0.4 ppm 2 hours
Respiratory Symptoms	Healthy Subjects	0.12 ppm 6.6 hours	
Airway Inflammation	Healthy Subjects	0.2 ppm 4 hours	
	Asthmatics	0.2 ppm 6 hours	0.24 ppm 90 min NOEL 0.12 ppm 90 min
Increased Sensitivity to So2	Healthy Subjects	0.12 ppm 45 min	
Increased Sensitivity to Allergen	Asthmatics	0.25 ppm 3 hours	0.4 ppm

Controlled Exposure Studies

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APPENDIX 5 -
HEALTH EFFECTS OF RESPIRABLE PARTICLES

SUMMARY

Over the past decade, evidence that human exposure to inhaled respirable particles can result in significant increases in both morbidity and mortality has become overwhelming. The following literature review details the development of scientific awareness and understanding of adverse health impacts which have thus far been identified and replicated around the world. Widely dispersed populations around the world have been assessed and have shown similar response patterns in every instance where appropriate statistical analyses have been undertaken.

It is now possible to enumerate the adverse health effects that have, on epidemiological, clinical and toxicological grounds been currently identified as being causally related to short-term increases in ambient respirable particles (PM_{10}). These associated adverse health effects include:

- increases in total mortality ('all causes'), as well as in mortality from respiratory or cardiac disease, of the order of 1% for every 10 µg/m3 increase in PM_{10} levels.

- increases in hospital admissions for respiratory, and (probably) cardiac conditions,

- increases in hospital casualty and medical surgery visits for asthma and other respiratory conditions,

- increases in functional limitation as indicated by restricted activity days or, in the case of children, by increased frequency of absence from school,

- increases in the daily prevalence of respiratory symptoms, and

- small decreases in the level of pulmonary function in healthy children, and in adults with obstructive airways disease.

These observations are consistent across many studies and provide a cohesive picture in that there are effects on many different respiratory health outcomes, however there remain legitimate questions as to the causal nature of these associations. Many questions remain, and centre on major issues such as the plausibility of the possible/probable associations, details of exposure, proper disease classification and the use of inappropriate and/or inadequate statistical analytical methods.

Reviewed and edited by Dr Jonathan A Streeton, of Jonathan A Streeton Pty, Ltd.

There are population subgroups that are clearly more sensitive to PM_{10} exposure, in that they experience more severely adverse health effects for a given particle exposure. These subgroups include the elderly (as a whole) and those individuals suffering from pre-existing heart or lung disease. There is also evidence to suggest that young children may be more sensitive, leading to an increased frequency of respiratory tract infections, coughing, and wheezing.

There is satisfactory evidence at this time that PM_{10} pollution produced from natural or crustal sources is significantly less harmful than PM_{10} generated from combustion processes, although in situations of extreme exposure such as with volcanic eruptions, significant long term respiratory damage can result.

Statistical evidence at this time suggests that the observed adverse health effects of PM_{10} appear to occur independently of the presence of other pollutants such as ozone, nitrogen dioxide, and probably sulfur dioxide, although the reverse does not apply. There is evidence to suggest that PM_{10} can impact significantly as a major confounder on the observed responses to other pollutants such as those listed above, however there is no satisfactory evidence that the effects of PM_{10} are potentiated by other pollutants.

At the present time, there is no evidence, based on epidemiologic data, that threshold concentrations can be described for PM10 below which it is not possible to detect any population impacts. With progressive refinement of statistical method leading to increasing sensitivity of detection, the lowest observed effect levels have been steadily reducing in recent years.

There is no available evidence to give credence to the hypothesis that, for equal daily concentrations, high particle concentrations for brief periods are more harmful than relatively constant low level concentrations. Further research is required before any useful progress can be made towards establishing air quality goals or guidelines based on short-term exposures. At the present time, there it would seem that goals or guidelines based on 24-hour average measurements should be sufficient to adequately protect population health. An alternative option could be to base air quality goals or guidelines on increases in PM_{10} concentrations rather than on absolute PM_{10} concentrations. Focussing on the frequency of daily 10 $\mu g/m^3$ PM_{10} increments above an absolute concentration of 10 $\mu g/m^3$ is a starting point given the weight of current scientific evidence. This is the approach currently being considered by the WHO Working Group (Dr. R. Maynard, personal communication), and determination of the numbers of PM_{10} increments that might be considered acceptable has to be based on the acceptability (to the particular population in question) of the various health impacts health impacts predicted for the selected numbers of PM_{10} increments.

Currently, the evidence that particles of some particle size ranges ($PM_{2.5}$, $PM_{1.0}$) seen within the PM_{10} fraction might be more deleterious to health than

others size fractions is of varying strength, although there is increasing evidence to suggest that the $PM_{2.5}$ fraction (fine particles) may well be the major area of concern with regard to adverse health effects. With these emerging trends in mind, there would appear to be compelling reasons for basing ambient particle goals or guidelines on the fine particle fraction, rather than concentrating on the larger Inhalable particle fraction (coarse particles or PM_{10}). More recently, concerns are being raised as to the weighting that may or not be required to be put on smaller particle fractions such $PM_{1.0}$, or even smaller (ultrafine particles). At this stage of things, there is no supporting data to suggest that this fraction is necessarily of major concern in the long-term, certainly when compared to the clearly increasing role of the $PM_{2.5}$ fraction. Decisions regarding the size range of particles to be monitored will have major implications for the monitoring networks already in place.

There is no convincing evidence yet to hand which suggests that chronic health problems are being caused by long-term exposure to PM_{10} pollution, independent of the effects due to repeated short-term exposures. Longer term health effects may well be related to chronic exposure to other pollutants, such as NO_2, SO_2, and possibly O_3. There is at this time no compelling evidence to support a health based annual average air quality goal or guideline, although such a value may be of assistance in achieving longer term aesthetic goals. The main thrust for controls, based on health effects, must be towards a short-term objective. Indeed, there is good evidence to suggest that currently observed health effects are occurring at particle levels well below current annual standards.

World Health Organisation - European Region (WHO-EURO) has prepared revised Air Quality Guidelines for a various air pollutants, including particles. The earlier guidelines(1987) were based on the premise that there were no observable adverse effects levels (NOAELS)and that public health could be protected by establishing a lower concentration limit than the NOAEL using a safety factor. The latest WHO-EURO expert committee for particles concluded that there was no current basis for establishing a NOAEL for particles. It has recommended instead that exposure-response relationships for PM_{10} and $PM_{2.5}$. as interpreted and tabulated by the expert panel, be reported with tabular guidance and interpretive text for use by national authorities in establishing their own air quality standards. Thus, the burden of decision is put back on to the various national authorities to determine their own acceptance limits for the public health impacts of exposures to ambient respirable particles.

Another recent report from the U.K. (DoH 1995) concluded that "In terms of protecting public health it would be <u>imprudent</u> <u>not</u> to regard the demonstrated associations between daily concentrations of particles and acute effects on health as casual".

Finally, the most thorough and comprehensive report now available is the new US EPA Particle Criteria Document (US EPA 1996a-c; US EPA 1996d).

Among its numerous conclusions are:

- The chemical and physical differences between fine-mode and coarse-mode particles have important implications for evaluation of the health and welfare effects of such particles as distinct pollutant subclasses.

- Our current understanding of the toxicology of ambient particulate matter suggests that fine and coarse particles may have different biological effects.

- The evidence of PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, mis-specification or concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure other than PM, weather, or other variables, nor confounding of PM effects with effects of other factors.

- Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles, thoracic particles (PM_{10} or PM_{15}), and sulfate ($SO_4^=$). Less consistent relationships have been observed for TSP, strong acidity (H^+), and coarse PM (PM_{10} - $PM_{2.5}$).

- There is evidence that older adults with disease are more likely to be impacted by PM-related health effects (including mortality) than are healthy young adults. The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by :

  1. the more uniform distribution of fine particles across urban areas and their ell-correlated variation from site to site within a given city;

  2. the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time);

  3. the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

Other points include:

- Based on theoretical, experimental and observational scientific evidence, the pathogenic effects attributable to particles in the inhalable fraction are largely, and possibly exclusively, due to the effects of particles in the fine fraction.

- Based on the concentration-response relationships observed by $PM_{2.5}$ and for PM_{10} it is reasonable to maintain that adverse health effects related to increases in fine particle concentrations begin to occur at a concentration of approximately 20 ug/m3.

- A reasonable recommendation, if feasible, would be to base air quality objectives or standards on fine particle concentrations while maintaining the capability of monitoring concentrations of inhalable particles, with or without continuing to maintain objectives or standards based on inhalable particle concentrations as well.

- There is no strong evidence available at this time that fine particle objectives or standards should be base don averaging times shorter than 24 hours.

- Although there is historical precedent for objectives and standards based on annual average particle concentrations, there is no evidence that an annual average provides additional information of relevance to the adverse health effects of particles beyond that available from daily averages alone.

- Although there is some scientific support for fine particle chemical composition being important in determining pathogenic particle effects, the evidence that would support inclusion of some aspect of particle chemical composition in the fine particle objectives or standards, beyond that already accounted for by focusing on the fine fraction alone, is contradictory and therefore not compelling.

Suggested 'Protective' Ranges:

PM_{10}: 24 Hours: 50 μg/m³

$PM_{2.5}$: 24 hours: 20 - 25 μg/m³

NO 'ANNUAL' Range is proposed at this time.

Consideration could be given to the later introduction of a guideline/standard based on exposure - response relationships.

GENERAL LITERATURE REVIEW [#]

Introduction

It has been recognised for many years that high levels of air pollution can lead to increases in mortality and morbidity. Episodes of high concentrations of smog were associated with substantial increases in daily mortality in the Meuse Valley, Belgium 1930, Donora, Pennsylvania in 1948, and in London, England, 1952. The sudden large increases in sickness and death that accompanied such episodes demonstrated that air pollution can adversely affect human health. The rapid rise and fall in pollution levels, and a similar pattern in daily mortality counts, left little doubt that the high concentrations of smog were associated with excess mortality. In recent years there has been a large number of epidemiological studies analysing the associations between air pollution and mortality and increases in hospitalisations and respiratory symptoms. These studies have shown associations between mortality/morbidity and air pollution at levels well below current ambient air standards. These associations have been shown in many different communities worldwide. It has recently been shown (Pope et al, 1995) in a long-term prospective study of adults in the US that chronic levels of higher PM_{10} pollution are associated with increased mortality after adjusting for several risk factors . Daily fluctuations in PM_{10} levels have also been shown to be related to acute respiratory hospital admissions in children, to school and kindergarten absences, to decrements in peak flow rates in children, and to increased medication use in children and adults with asthma. The most sensitive groups to the effects of particulate air pollution appear to be the elderly and children with existing disease. Although some epidemiologic studies suggest that acid aerosols are an important toxic component of PM_{10}, other studies do not support this hypothesis.

The major effects of concern with regard to airborne particles can be summarised as follows:

- Increased Mortality
- Aggravation of Existing Respiratory and Cardiovascular Disease
- Hospital Admissions and Emergency Department Visits
- School Absences
- Work Loss Days
- Restricted Activity Days
- Respiratory Mechanics and Symptoms
- Altered Lung Clearance and Other Host Defence Mechanisms
- Morphological Damage
- Cancer

[#] Prepared by Dr. Lyn Denison, PhD., EPA Victoria, initially as part of a contract for ANZEEC, and gratefully incorporated into this review with their kind permission. The ANZEEC review has since been enlarged with the addition of more recent material, and edited jointly by Dr. Lyn Denison and by Dr. Jonathan Streeton, FRACP.

The majority of effects listed above have been consistently linked with exposure to particulate matter from a large body of epidemiological evidence. Epidemiological studies identify site-, time- and monitor specific associations of incidence of diseases or effects and risk factors; they do not demonstrate causality or provide clear evidence of the mechanisms of such diseases or effects. Specifically, epidemiological studies focus on showing whether associations exist, rather than how they might be explained at a pathogenic or mechanistic level. Animal studies and experimental exposure, or chamber, studies with humans help to generate data from which hypotheses concerning the mechanisms for the effects of particulate matter which in turn can aid in the design of epidemiological studies.

Despite the findings from the epidemiologic studies, there are no complementary data from toxicologic studies or from acute human exposures to similar levels of respirable particles. Controlled human exposure to various particles ($< 150 \ \mu g/m^3$) in US studies have not identified significant alterations in respiratory function in healthy individuals. Typically, experimental animal toxicology studies are designed to help develop information for understanding the mechanistic steps following particle deposition and health effects from specific constituents of the particulate matter. Qualitative support for the epidemiologic findings has been reported (UK Department of Health, 1995) for specific components of the ambient particulate matter in controlled clinical studies of humans as well as animals. For such studies, the biological responses occurring in the respiratory tract following inhalation of respirable particles encompass a continuum of changes including: respiratory symptoms such as wheeze and cough, changes in pulmonary function, altered mucocilliary clearance, inflammation, changes in lung morphology and tumour formation. In the vast majority of studies, however, results were observed only at concentrations of specific substances or simple mixtures that are significantly higher than those found in urban atmospheres. These limitations hinder the interpretation of this work with regard to determining either the risk of adverse effects from particles in humans or in determining the mechanism of action of particles at ambient levels. Caution needs to be exercised when interpreting these results as particles generated in a laboratory are probably not an accurate reproduction of the complex physico-chemical characteristics of particles found in ambient air along with varying amounts of pollutant gases (Sioutas et al., 1995). The lack of an effect of any one of the chemical constituents of particulate matter in experimental systems may be due to the fact that responses to differing components of mixtures may be synergistic, additive, or antagonistic, and may vary with particle size and surface characteristics. However, these studies do illustrate the potential for particles to cause adverse effects and aid in the development of proposed mechanisms for observed effects. For example, studies to date have indicated that the site of respiratory tract deposition (and hence particle size) clearly influences health outcome and that toxicity can vary greatly by chemical species (eg. cadmium toxicity differs from that of sulphuric acid).

Mortality Studies

Reports on the effects of ambient particulate matter on health date back to the dramatic pollution episodes of Belgium's industrial Meuse Valley; Donora, Pennsylvania; and London, England. In these cases winter weather inversions led to very high particle concentrations which were associated with increases in mortality and morbidity, especially among individuals with preexisting cardiopulmonary conditions. Analyses of a series of episodes in London indicated excess mortality occurring with abrupt increases in particle levels accompanied by high levels of SO_2. Since then extensive time-series analysis has been carried out to examine the particulate pollution/mortality relationship across 14 London winters (US EPA, 1982). These studies differed from the original studies by examining the mortality/particle relationship using more sophisticated statistical techniques to examine mortality during routine variations in particle levels and sulphur dioxide levels. These analyses showed a continuum of response across particulate levels beginning at 20 $\mu g/m^3$ and suggested effects from exposure to particulate matter occurred at levels more similar to those observed in Australia and the US. These studies did not conclusively distinguish the effects of particulate matter from those of SO_2.

More recent studies have consistently shown an association between short-term exposure to particulate matter and mortality. In these studies investigators have observed an association between daily or the average of several days concentrations of particulate matter (as TSP, PM_{10} or $PM_{2.5}$) and mortality in many locations worldwide. Most of the studies to date come from the USA and a very limited number in Australia. These studies are consistent with earlier studies in London, but extend to lower concentrations and a large number of areas with differing climate, particle composition, and varying amounts of SO_2 and other gaseous pollutants.

During a high pollution episode in London in 1952, 4,000 excess deaths occurred, 2,000 in London County (Bascom et al, 1996). Maximum 24 hr particulate levels (measured as Black Smoke) reached as high as 4,000 $\mu g/m^3$ whilst SO_2 levels averaged at 0.95 ppm (maximum 24 hr mean of 1.5 ppm). In December 1962 a similar episode took place, however, in this episode only 350 excess deaths were noted in London County. In this episode particulate levels were only 20% of the 1952 levels while SO_2 levels were similar to those observed in the previous episode with an average value of 0.80 ppm (maximum 24 hr mean level of 1.5 ppm). The fact that SO_2 levels were similar in both episodes while both particle levels and excess deaths were significantly lower suggests that the deaths were closely associated with particle levels.

A reanalysis of the data from 14 London winters (Ostro, 1984) was conducted to establish the existence of a threshold in the particle/mortality relationship. Over this period mean Black Smoke levels ranged from 552 $\mu g/m^3$ in 1958-59 to 60 $\mu g/m^3$ during the winter of 1971-72. This data set consists of daily

measurements of particulates and has played a central role in the determination of the association between particulates and mortality. The results of this study indicated that after controlling for temperature and humidity, a strong association between Black Smoke and mortality existed at levels below 150 $\mu g/m^3$. In addition, this association existed even during winters that were non-episodic. No evidence of a threshold level was observed. A further study (Schwartz and Marcus, 1990) using time-series analysis confirmed the findings of Ostro. An association was observed between Black Smoke levels and mortality at levels as low as 20 $\mu g/m^3$. The slope of the relationship was found to be steeper at lower levels and decreased at higher levels. In this study SO_2 levels were included in the model. The results indicated that the relationship between SO_2 and mortality was much less stable than Black Smoke and mortality. In the absence of Black Smoke the association was highly significant, however with Black Smoke included in the model, the association between SO_2 and mortality was substantially reduced and non significant. The correlation between Black Smoke and mortality remained highly significant, independent of any effect of SO_2.

A more recent study has evaluated the association between Black Smoke and mortality in London between 1987 and 1992 (Anderson et al, 1996). This study found strong associations between Black Smoke and mortality with a relative risk of increased mortality from all causes of 1.1% per 10 $\mu g/m^3$ increase in Black Smoke levels. These Black Smoke levels are approximately 25 times lower than those observed during 1958-59. Mean 24 hr Black Smoke levels were 14.6 $\mu g/m^3$. The strongest association was found for a 1-day lag period. There was no difference found in the association between all cause, respiratory or cardiovascular mortality and Black Smoke levels. Associations were also found for daily mortality and ozone, NO_2 and SO_2, however, the observed effects were smaller than those for Black Smoke.

Early studies from the US utilised a variety of measures of airborne particulate matter. Coefficient of Haze (COH), an optical measure of fine particles, has been used in studies in both New York and Santa Clara County, California (Glasser and Greenberg, 1971; Fairley et al, 1990). Daily mortality in New York City for the winter months (October through March) during the 5 year period 1960 to 1964 was found to be associated with COH and SO_2 levels. Further studies from New York during 1963 to 1972 (Schimmel et al, 1972) showed that 2.8% of deaths during this period were attributable to air pollution. Further studies conducted in Santa Clara County using COH measurements (Fairley, 1990), found that after controlling for temperature, humidity, year and seasonality an association was found between high particulate concentrations and mortality. Mortality from respiratory disease was found to be the most strongly associated to COH levels. One important feature of this study is that SO_2 levels in Santa Clara County are low. This allows the effects of particulate air pollution to be separated from those of SO_2 assuming that there is a threshold for the effects of SO_2.

Daily total mortality has also been associated with TSP concentrations. Analysis of data from Steubenville, Ohio, for 1974 to 1984, showed a statistical significant increase in daily total mortality associated with TSP levels on the previous day (Schwartz and Dockery, 1992a). This association persisted after controlling for season and temperature. Mean TSP levels were 111 $\mu g/m^3$ and SO_2 28 ppb. A significant association was also found for SO_2 and daily mortality. The association was less significant than the association with particulates, and became insignificant when particulates were simultaneously included in the model. The association with TSP however was independent of the SO_2 concentrations. The Steubenville data is one of the few data sets in the US that incorporates daily measurements of airborne particulates.

A reanalysis of the Steubenville data (Moolgavkar et al., 1995a) has shown quite different results. In this study full year mortality was analysed and it was found that with the inclusion of SO_2 in the model, the association between TSP and mortality was markedly reduced and became statistically insignificant. A similar result was obtained when the mortality data was analysed by season. These authors also found that the association between particulates, SO_2 and mortality was also seasonal. The conclusion from this reanalysis was that on the basis of this data it was premature to isolate any particular component of air pollution as being responsible for the increase in mortality. The difference observed between the two studies may be due to small differences in the data sets used (Moolgavkar et al, 1995a) and raises the question as to the effect of small perturbations in the data in the models used.

A time series analysis of data from Philadelphia between 1973 and 1980 (Schwartz and Dockery, 1992b) found that after controlling for the effects of temperature and dew point, a statistically significant association was found between TSP and all-cause mortality. The association was significant for populations under 65 yrs and over 65 yrs of age, however the association was stronger in the older age group. Mean TSP levels were 77.2 $\mu g/m^3$. Associations were also found for SO_2 and all-cause mortality, however the association was smaller than that observed for TSP and did not persist when both pollutants were considered simultaneously in the model. Total mortality was found to increase by 7% with each 100 $\mu g/m^3$ increase in TSP. Cause specific mortality was also investigated and found to be associated with TSP. For each 100 $\mu g/m^3$ increase in TSP the following increases in cause specific mortality were noted: Chronic obstructive pulmonary disease, 19%, pneumonia, 11% and cardiovascular disease 10%. The dose response relationship observed in this study indicated that the association between mortality and TSP was not restricted to high TSP days but was continuous across the range of TSP concentrations.

A second study conducted in Philadelphia (Schwartz, 1994a) compared daily mortality on high pollution days with daily mortality on low pollution days for the period 1973-1980. Mean TSP levels on high pollution days were 141 $\mu g/m^3$

versus 47 μg/m³ on low pollution days and weather patterns were similar for both the high and low pollution days. There was an 8% increase in daily deaths observed on high pollution days compared to low pollution days. A 25% increase in death from Chronic Lung Disease, 13% increase in death from pneumonia and a 9% increase in death from cardiovascular disease were also observed. An increase of 19% was noted for lung cancer deaths, a much larger effect than that noted by Schwartz and Dockery, 1992b). The results of the study by Schwartz (1994a) confirms that findings of Dockery and Schwartz (1992b) that the increased risk of death was greater for the elderly and for deaths from COPD, pneumonia and cardiovascular disease. This is consistent with airborne particles acting as an irritant to exacerbate preexisting conditions, particularly respiratory conditions.

Two subsequent studies have been conducted on the association between daily mortality and TSP levels in Philadelphia (Li and Roth, 1995; Moolgavkar et al, 1995b). A study by Li and Roth (1995) has analysed the daily air pollution and mortality data between 1973 and 1990. These analyses included TSP, O_3 and SO_2 as well as a variety of meteorological data. Several statistical methods were used on the same data sets to ascertain the impact of the model on the strength of the observed association. The main findings from this study were that the association between daily mortality and TSP was highly dependent on the statistical method applied, seasonal variations, the number of pollutants in the model and whether interactions between pollution variables and weather were considered. Depending on the model used both positive and negative associations between daily mortality and TSP levels were observed. The results of this study are summarised as follows:

1. Even in models with the greatest explanatory power, 18% of the variation in daily mortality could be explained with weather variables and seasonality being the strongest predictors. In analyses using weather alone, about 14% of the variations in daily mortality could be explained, but in models using pollution alone, less than 5% could be explained. Also, in a two stage analysis where weather variables are forced into the model and pollution is left to explain the residual, pollution accounts for less than 1% of the variation.

2. The fact that weather and pollution variables are highly correlated with each other makes it difficult to separate out the effect of one pollution variable from another and the effect of weather from pollution. Thus it is difficult to say with any certainty whether the significant associations between TSP and daily mortality observed in this study were real or surrogate behaviour for some other pollutant or weather variable.

3. The analysis by season showed no consistent significant association between TSP and mortality. For older people (ie., 65 yrs +), this relationship was significant only in the winter in the case where other pollutants were not considered. In contrast, for younger people (ie., under 65 yrs),

the relationship was significant only in the spring in the case where other pollutants were not considered. In both cases TSP was insignificant when more than one pollutant was taken into account.

4. Analyses broken down by cause of death indicated many negative results, but the associations were never statistically significant.

The overall conclusion from this study was that the results of the analyses did not point to a clear association between daily mortality and particulate matter or to any other pollutant. For almost every result suggesting a positive association between particulate levels and daily mortality, there were negative or nonsignificant results pointing the other way.

This study also raised an important issue regarding the appropriate methods for analysing air pollution and daily mortality data. Using models that have previously been used in other studies, such as Poisson models, regression models and autoregressive models, results ranging from positive to negative associations have been obtained. Given the range of methods applied in epidemiological studies, care must be taken when interpreting these results. It was unclear from this study which statistical model generated the most definitive results.

A study by Moolgavkar and coworkers (1995b) analysing data from Philadelphia between 1973 and 1988 supports the findings of Li and Roth (1995). Using a Poisson regression model the effects of TSP, O_3 and SO_2 on daily mortality were examined. The results of this study indicated that SO_2 was associated with daily mortality during the spring, autumn and winter months, and TSP and O_3 were associated with daily mortality in the summer. With the inclusion of other pollutants in the model the strength of the association was weakened. This study analysed data for each season separately, whereas the previous by Schwartz and Dockery (1992b) did not and used indicator variables to control for season. Moolgavkar et al (1995b) suggest that this may explain some of the differences between the two studies. In response Dockery and Schwartz (1995) suggest that controlling by season is a case of overcontrol which is biasing the results. These authors also suggest that the data used by Moolgavkar is confounded by long-term trends. Moolgavkar et al (1995b) conclude by suggesting that the association between daily mortality and air pollution cannot be explained by any one agent.

It should be noted that the mortality data used in these studies were quite different. Schwartz and Dockery considered deaths of residents of Philadelphia only. In the study by Moolgavkar, a data set that incorporated all deaths including those of persons not residing in Philadelphia at the time was used.

Moolgavkar and others have suggested that the association between particulate air pollution and increased mortality may be biased (Moolgavkar et al., 1995a; Moolgavkar et al, 1995b; Li and Roth, 1995; Styer et al, 1995). Three concerns have been raised about the original analyses: (1) errors may have been present in the analytic data sets; (2) the results of the study may be sensitive to analytic methods; (3) confounding variables may not have been appropriately controlled. In response, the Health Effects Institute (Samet et al, 1995) in the US undertook a reanalysis of selected studies of particulate air pollution and daily mortality by an independent team of epidemiologists and biostatisticians. Specific attention was given to studies of daily mortality and air pollution associations in Philadelphia, in part because of the multiple studies of these data. Both the data sets from the Schwartz and Dockery study (1992b) and the Moolgavkar study (1995b) were reanalysed. In general, the reanalyses supported the findings of the original authors. For the data set of Schwartz and Dockery, an association was found between daily mortality and TSP levels. This association was not due to confounding by weather, season or time trends. In contrast however to the original study, the effects of SO_2 were not able to be separated from TSP in the reanalysis. Using the data set of Moolgavkar et al, the reanalysis supported the findings of the original study.

A study from Detroit, Michigan used TSP data from every six day sampling and airport visibility data to assess the association between daily mortality and particulate matter (Schwartz, 1991) between 1973 and 1982. Daily TSP levels were estimated using a predictive model for TSP. Mean TSP levels (predicted) were 87 $\mu g/m^3$. A significant association was found between predicted TSP levels and daily mortality with a 6% increase in daily mortality observed per 100 $\mu g/m^3$ increase in TSP. The correlation was independent on SO_2 but not vice-versa.

Studies conducted in St Louis, Missouri, and Kingston/Harriman in Eastern Tennessee (Dockery et al, 1992) found significant associations between daily total mortality and PM_{10} levels for a 1 yr period between September 1985 and August 1986. Total mortality in St Louis was found to increase 16% per 100 $\mu g/m^3$ increase in PM_{10} and in eastern Tennessee by 17% per 100 $\mu g/m^3$. Positive but weaker associations were also found for $PM_{2.5}$, sulphate and aerosol acidity in both locations. No association was found for SO_2, NO_2 or ozone and daily mortality. With the exception of acidity, which was higher in eastern Tennessee, pollutant levels were similar at both locations with mean PM_{10} levels of 27.6 $\mu g/m^3$ and 30 $\mu g/m^3$ for St Louis and eastern Tennessee respectively, and $PM_{2.5}$ levels of 17.7 $\mu g/m^3$ and 21 $\mu g/m^3$. Mortality in St Louis was found to be 5% higher in the winter months. In eastern Tennessee mortality was elevated on hot, humid and in the winter. In the St Louis study, particulate elemental concentrations, in particular aluminium, calcium, chromium, iron and silica, were all correlated with PM_{10} and had a positive association with mortality. In eastern Tennessee, associations between mortality and the same elements were positive but nonsignificant.

Insights on whether particulates or SO_2 are responsible for the observed increases in daily mortality has recently been provided by studies conducted in the Utah Valley (Pope et al, 1992). This area is characterised by high concentrations of particles (daily maximum PM_{10} of up to 365 μg/m³) and low concentrations of SO_2 (daily maxima of 0.02 ppm). During winter temperature inversions, air pollutants are trapped near the valley floor and high concentrations of PM_{10} result. The main source of PM_{10} in the region is a steel mill which when in operation emits 82-92% of the valley's industrial PM_{10}. During the period 1985 to 1989, daily mortality was 11% higher on days when PM_{10} was greater than 100 μg/m³ than on days when PM_{10} was less than 50 μg/m³. After controlling for meteorologic and seasonal factors, an increase in 5 day mean PM_{10} levels by 100 μg/m³ was found to be associated with a 16% increase in deaths per day. The association with mortality and PM_{10} was largest for respiratory disease, followed by cardiovascular disease.

During the period of this study the steel mill, the main source of PM_{10}, was closed due to a strike. The average PM_{10} levels during the period that the mill was closed were 35 μg/m³ and while the mill was open 50 μg/m³. Average daily deaths during the period when the mill was open were 3.2% higher than during the period when it was closed, adding support to association between PM_{10} and mortality.

A more recent study utilising the data from the Utah Valley between 1985 and 1992 (Lyon et al, 1995) confirmed the finding of Pope et al. On further analysis no statistically significant association was found between increased mortality and exposure to PM_{10} for individual years. The strongest association was observed in the spring. These authors suggested that the association between PM_{10} and acute mortality may not be causal, and may be related to a confounding factor not adequately controlled in previous studies.

A study conducted in Birmingham, Alabama, using data from 1985 to 1988 found a significant associationμbetween PM_{10} and daily mortality with an 11% increase in mortality per 100ug/m³ (Schwartz, 1994b). No evidence of a threshold was observed down to the lowest PM_{10} levels, approximately 20 μg/m³. The relative increase in mortality was higher for respiratory and cardiovascular deaths and lower for all other causes. Mean PM_{10} levels were 47.9 μg/m³ with a maximum value of 163 μg/m³. Particle levels in this study were highest during the summer months.

The data sets from the Birmingham, Santa Clara and Utah studies were all reassessed by the Samet and coworkers as part of the Health Effects Institute study (Samet et al, 1995). This reanalysis confirmed the findings of the original studies adding further support to the ever growing body of literature associating particulate air pollution with increases in daily mortality.

Although many studies find constant associations between increased risk of mortality and airborne particles, several studies are still finding conflicting

results. A recent study (Styer et al, 1995) investigated the associations between daily mortality and PM_{10} in Cook County, Illinois, and Salt Lake County, Utah. Using the same analysis, there was an association found between PM_{10} in Cook County during the spring and autumn, however no association was found in Salt Lake County. The differences may be due to a variety of factors including sample size; daily deaths were 126.7 and 10.2 in Cook County and Salt Lake County respectively. PM_{10} levels were higher in Salt Lake County than in Cook County with median values of 48 and 38 $\mu g/m^3$ respectively. Maximum PM_{10} levels for Cook County reached 365 $\mu g/m^3$ and for Salt Lake County 194 $\mu g/m^3$. Other differences that may have an effect are differences in populations, differences in the chemical and physical characteristics of the PM_{10}, or possibly differences in the weather that were not adequately controlled for in the model. Strong associations were found between PM_{10} and weather in both counties and it is generally accepted that weather conditions affect mortality rates.

The conclusion of these authors was that the association between PM_{10} and daily mortality was inconsistent, and is in contrast with other studies that do show consistency in the association between quite different locations. It should be noted that statistically significant correlations were previously found between PM_{10} and hospital admissions for respiratory disease in Salt Lake County (Pope, 1991).

A further study from Cook County, Illinois, (Ito et al., 1995), showed a strong association between PM_{10} levels and daily mortality. When daily PM_{10} levels were averaged over all sites, the relative risk per 100 $\mu g/m^3$ PM_{10} was 1.06. Stronger associations were observed for an individual site within Cook County. The strength of the observed association was dependent on the amount of available data at each site. PM_{10} sampling was conducted on an every six day cycle, and some sites had only a small amount of data available (n≈300). These authors suggest that the variation between sites may be due in part to this small sample number and that this raises concern regarding the potential for compromised statistical power for short-term (<6 yr) studies when data from every six day sampling is used. The associations observed for Los Angeles County were weaker than those observed for Cook County, even though PM_{10} levels were higher in Los Angeles County. The results from this study indicate that the choice of PM_{10} sites can make a difference in the degree of significance reported in health effects analysis. Averaging over multiple PM_{10} sites appeared to increase the level of the significance of the mortality-PM_{10} association, even when individual sites did not approach significance. However, in some cases individual sites gave more significant results than for the multisite average.

The six cities study (Dockery et al, 1993), a prospective cohort study, investigated the long-term effects of air pollution on mortality for a group of 8111 adults aged between 25 and 74 yrs of age for the period 1974-90. The cities studied had significantly different levels of airborne particles ranging from an average of PM_{10} of 18.2 $\mu g/m^3$ in Portage, Wisconsin, to 46.5 $\mu g/m^3$ in

Steubenville, Ohio. After controlling for smoking and other risk factors such as age, weight, educational level etc, strong associations were found between mortality and levels of PM_{10}, $PM_{2.5}$ and sulphate particles. The observed association was related to pollution levels in each city and was strongest in the most polluted city. Associations were found for death from lung cancer and cardiopulmonary disease but not from other causes considered together. The strongest associations were found for fine particles ($PM_{2.5}$ and sulphates). The adjusted mortality-rate ratios between the least and most polluted cities, were found to be 1.26 (all cause), and 1.37 (lung cancer or cardiopulmonary disease).

One of the largest studies to date investigating the chronic effects of particulate matter on mortality is a prospective study carried out between 1982 and 1989 in 151 metropolitan areas in the US (Pope et al, 1995). This study relied on data for 552,138 men and women drawn from the American Cancer Society (ACS) Cancer Prevention Study II, an ongoing prospective mortality study of approximately 1.2 million adults. An association between mortality and fine particle levels, $PM_{2.5}$, was observed and this association persisted after controlling for age, sex, race, cigarette smoking, cigar and pipe smoking, exposure to passive cigarette smoke, occupational exposure, education, body mass index, and alcohol use. The associations held for all-cause and cardiopulmonary mortality. Lung cancer appeared to be more strongly associated with sulphate levels than with fine particles. Estimated pollution-related mortality risk was as high for never smokers as it was for ever smokers and as high for women as for men. These authors estimated that 8 deaths per year per 100,000 persons were associated with fine particulate air pollution. A difference of between 15 and 17% in mortality risks was observed between the least and most polluted cities, a range of mean concentrations from 9 to 33.5 $\mu g/m^3$.

The association between daily mortality and airborne particles has not only been observed in the US and London. Many studies from other parts of the world with varying climates and socioeconomic conditions also show strong associations. An ecological study conducted in the Czech Republic between 1986 and 1988 has found weak positive associations between neonatal mortality and both PM_{10} and TSP (Bobak and Leon, 1992). Stronger associations were seen for postneonatal mortality with a consistent increase in risk from the lowest to the highest quintile of PM_{10}. Mean PM_{10} levels were 68.5 $\mu g/m^3$ during the study period. A more recent study (Bachárová et al, 1996) in the Slovak Republic found no association between TSP levels and either total or cause specific mortality. Mean TSP levels during the study period were 80 $\mu g/m^3$ with maximum values reaching 720 $\mu g/m^3$. One explanation for this lack of association may be the small study population and lack of air monitoring data.

A further study investigating the effect of particulate air pollution on infant mortality was carried out in Rio de Janeiro for 1980 (Penna and Duchiade, 1991). This study found that after controlling for various socioeconomic

factors, a statistically significant association PM_{10} levels and infant mortality from pneumonia was found. Mean particle levels of 80 $\mu g/m^3$ were observed. A similar study carried out in Sao Paulo, Brazil (Saldiva et al, 1994), assessing the effects of air pollution and mortality from respiratory disease in children under 5 yrs of age between 1990 and 1991, found no association between PM_{10} levels and daily mortality. PM_{10} levels were similar to those observed in Rio de Janiero, with a mean value of 82.4 $\mu g/m^3$. There was however a strong association (30% increase) between daily mortality from respiratory disease and NO_x levels.

A recent study conducted in Santiago, Chile, (Ostro et al., 1996) has found strong associations between daily mortality and daily PM_{10} levels. A 10 $\mu g/m^3$ increment in daily average PM_{10} was associated with a 1% increase in mortality. The association was robust to changes in the model and the inclusion of other pollutants. The mean PM_{10} level during the study period was 115.4 $\mu g/m^3$ with a maximum value of 500 $\mu g/m^3$. Levels were higher during the winter months. The mean 24 hr value during the winter months was 141.5 $\mu g/m^3$. The strongest associations were found for total mortality, mortality from respiratory disease, and mortality for males and the elderly. When considered alone both SO_2 and NO_2 were associated with total mortality. However, when PM_{10} was added into the model, none of the other pollutants were statistically significant.

Several studies have been conducted throughout Europe, the most recent coming from the APHEA study (Katsouyanni et al, 1995). The APHEA project was supported by the European Union Environment 1991-94 Programme. This programme involved studies in 15 European cities using a standardised approach for data analysis. Estimates of short-term health effects, including mortality and hospital admissions, of air pollution were determined for the cities of Amsterdam, Athens, Barcelona, Bratislava, Cracow, Helsinki, Kohln, Lodz, London, Lyon, Milan, Paris, Poznan, Rotterdam, and Wroclaw. Substantial variations in air pollution levels, mixtures and patterns as well as climatic conditions exist between all of these cities. Results from the analysis of mortality and air pollution data in Athens found strong associations between Black Smoke, SO_2 and CO levels and daily total mortality (Touloumi et al, 1996). For an increase of 100 $\mu g/m^3$ in SO_2 and Black Smoke levels there were corresponding increases of 12% and 5% respectively in total mortality. The association with SO_2 was found to be sensitive to Black Smoke levels with a stronger effect being observed on days when Black Smoke levels were high. The effect of Black Smoke however was not sensitive to fluctuations in SO_2 levels. The association with SO_2 was seasonal with the strongest effects observed in the winter months when SO_2 levels were highest. Mean Black Smoke levels for the study period were 84.4 $\mu g/m^3$ with a maximum of 333 $\mu g/m^3$. A time-series analysis of the short-term effects of Black Smoke levels on daily mortality in Athens for the period 1984-1988 (Touloumi et al, 1994) showed non-linear monotonically increasing relationships. The slopes of the exposure-response curves were steeper at lower air pollution levels. Associations with SO_2, CO and daily mortality were

also observed. Mean smoke levels averaged across all stations were 82.9 μg/m^3; mean levels for CO and SO$_2$ were 5.8 mg/m^3 and 44.9 μg/m^3 respectively. An earlier study investigating associations between air pollution and cause specific mortality in Athens (Katsouyanni et al, 1990) found weak correlations between air pollutants, Black Smoke and SO$_2$, and daily mortality. Mortality was generally higher on high pollution days, and the difference was more significant for respiratory conditions. No attempt was made to differentiate between the effects of the two pollutants. The observed associations were found in people over the age of 75 yrs and in infants. Mean Black Smoke levels ranged from 41 to 73 μg/m^3 with maximum levels reaching as high as 790 μg/m^3.

In January 1985, a smog episode occurred in West Germany which persisted for 5 days (Wichmann et al, 1989). Average 24 hr levels of suspended particulates reached as high as 600 μg/m^3 during this period compared to a control area where average levels were 190 μg/m^3. Increases in the total number of deaths in the affected area was 8% compared with only 2% in the control area. the effects noted were more pronounced for cardiovascular diseases than for respiratory diseases. A more recent study in Köln, Germany for the period 1975-85, has also found associations between daily mortality SO$_2$, TSP and PM$_7$ (Spix and Wichmann, 1996). Both measures of particulates were associated with a 2% increase in total mortality while SO$_2$ levels were associated with an increase of 3-4% in mortality. Effects were usually observed after a one-day lag period. Mean PM$_7$ levels during the study period were 34 μg/m^3 with a maximum of 239 μg/m^3. Mean TSP levels were 68 μg/m^3 with a maximum value of 304 μg/m^3, much lower than in the previous study.

A study from Lyon, France (Zmirou et al, 1996) investigated the association between PM$_{13}$ and cause specific death for the period 1985-90. Four categories of cause specific death were studies: total (minus external causes), respiratory, cardiovascular and digestive causes (as a control condition). Significant associations were found for SO$_2$ and PM$_{13}$ and mortality from respiratory and cardiovascular conditions. The association for SO$_2$ was stronger than that observed for PM$_{13}$. Mean PM$_{13}$ and SO$_2$ levels were 38 μg/m^3 and 100 μg/m^3 respectively. Maximum levels reached as high as 180 μg/m^3 and 636 μg/m^3 for PM$_{13}$ and SO$_2$ respectively. The relative risks associated with a 50 μg/m^3 increment of PM$_{13}$ were 1.04 for respiratory and cardiovascular deaths. The effects of particulates was slightly increased during the winter months. The association with SO$_2$ was enhanced when particulate levels were greater than 60 μg/m^3. No association was found between any pollutant and digestive mortality.

Black smoke and SO$_2$ levels were found to be associated with increases in total, elderly, respiratory and cardiovascular mortality in Barcelona, Spain, for the period 1985-91 (Sunyer et al, 1996). Relative risks for a 100 μg/m^3 increase in Black Smoke levels were 1.07 for total mortality, 1.06 for elderly mortality, 1.10

for respiratory mortality and 1.09 for cardiovascular mortality. Associations with SO_2 were stronger than with particles. The associations with Black Smoke did not vary with season. Twenty four hour Black Smoke levels ranged from 10.6 to 126 $\mu g/m^3$ with SO_2 levels ranging from 2.2 to 160 $\mu g/m^3$. Levels of SO_2 and Black Smoke were highest during the winter months.

The use of Black Smoke measurements as a surrogate for PM_{10} in health studies has recently been questioned (Muir and Laxen, 1995; Mage, 1996; Horvath, 1996). The main question centres around the nature of the particles that are measured by the Black Smoke method compared with gravimetric determinations of PM_{10}. As Black Smoke is a measure of the blackness of a filter, it may not be a true indicator of total particles in the respirable range. It has been noted that the relationship between PM_{10} and Black Smoke is different in the summer compared to winter (Muir and Laxen 1995). This is thought to be due to the fact that particulates are lighter in colour during the summer and therefore are not measured by the Black Smoke method (Horvath, 1996). This means that Black Smoke readings are dominated by carbon particles and other species such as ammonium sulphate, metals etc. are ignored. It would appear that until the toxicology of particulate matter is resolved care must be taken when assessing the associations between mortality and Black Smoke levels. This is probably more critical during the summer months when discrepancies between PM_{10} and Black Smoke levels have been observed.

This body of results discussed above has been viewed by many with scepticism. One of the main concerns is the lack of biological plausibility. It is difficult to understand how a 10 $\mu g/m^3$ increase in PM_{10} levels could result in a 1% increase in daily mortality. Further there is no animal toxicology data for particulate matter that suggest significant biological mechanisms that could account for health effects at the low levels of exposure encountered in the population based studies. The other principal concern has been that the results may be due to an artefact of the statistical analysis methods that have been used in the most recent literature on this topic. Kinney et al (1995) carried out a series of analyses using different statistical methods on the same data base to investigate the sensitivity of the mortality/PM_{10} relationship. This study used daily mortality and air pollution data from Los Angeles. The PM_{10} data was collected on a six daily cycle with values ranging from 15 to 177 $\mu g/m^3$. Mean levels were 58 $\mu g/m^3$ .The results of this study found that the relationship was only mildly sensitive to alternative statistical methods. There was no difference observed between an ordinary least squares and Poisson models. A relative risk of 1.05 per 100 $\mu g/m^3$ increase in PM_{10} was found for all analyses.

Lipfert and Wyzga (1995) analysed the results of 31 studies linking air pollution and mortality. The conclusion from their analysis was that although consistent positive associations between mortality and various measures of air pollution (including TSP, PM_{10}, $PM_{2.5}$, COH, and SO_4^{2-}), it is not possible to identify a

specific exposure-response relation for any one pollutant. Lack of appropriate data on personal exposures was thought to be a critical limitation in this regard. In addition, the authors believed the relative health importance of the constituents of ambient air cannot at this stage be identified with certainty. Some air pollutants have been investigated more thoroughly than others, but since none exist in isolation, the possibility of shared associations could not be ruled out by these authors. A similar conclusion was reached by Ostro (1993) in an analysis of a number of studies from various locations. The conclusion from this study was that although many questions are still unanswered with regard to a cause-effect relationship, it is clear that particulate matter, or some pollutant to which it is correlated, appears to be strongly and consistently associated with increases in mortality. In addition, a separate mortality effect from SO_2, independent of particulate matter, may also exist.

A summary of the studies using a variety of indicators for particulate matter are shown in Table 1 of this Appendix. These studies have reported a consistent association between changes in particulate levels and mortality. Many of these studies have employed data from various samplers that yield different measures of particulate matter such as COH, Black Smoke, TSP, PM_{10}, and $PM_{2.5}$.

TABLE 1
Summary of Particulate Mortality Studies Worldwide.

LOCATION AND PERIOD	PARTICULATE MEASURE	MEAN PM_{10} ($\mu g/m^3$)	% CHANGE IN MORTALITY FOR EACH 10 $\mu g/m^3$ IN PM_{10}	REFERENCE
Total Mortality				
St Louis, MO 1985-86	PM_{10} previous day	28	1.5% (0.1%, 2.9%)	Dockery et al, 1992
Kingston, TN 1985-86	PM_{10} previous day	30	1.6% (-1.3%, 4.6%)	Dockery et al, 1992
Santa Clara, CA 1980-82, 84-86	Coefficient of Haze	35	0.8% (0.2%, 1.5%)	Fairley, 1990
Philadelphia, PA 1973-80	TSP (2 day mean)	40	1.2% (0.7%, 1.7%)	Schwartz and Dockery, 1992a
Birmingham AL 1985-88	PM_{10} (3 day mean)	48	1.0% (0.2, 1.9%)	Schwartz, 1993
Utah Valley, UT 1985-89	PM_{10} (5 day mean)	47	1.5% (0.9%, 2.1%)	Pope et al, 1992
Detroit, MI 1973-82	TSP	48	1.0% (0.5%, 1.6%)	Schwartz, 1991
Steubenville, OH 1974-84	TSP (previous day)	61	0.7% (0.4%, 1.0%)	Schwartz and Dockery, 1992b
Lyon, France 1985-90	PM_{13}	38	1.0%	Zmirou et al, 1996
Athens, Greece 1987-91	Black Smoke	84.4	0.5%	Touloumi et al, 1996
Barcelona, Spain 1985-91	Black Smoke	42.4	0.7%	Sunyer et al, 1996
Bratislava, Slovak Republic 1987-91	TSP	89.4	0.8%	Bacharova et al, 1996
Koln, Germany 1975-85	TSP PM_7	68 34	0.2% 0.2%	Spix et al , 1996
Los Angeles,CA 1985-90	PM_{10}	58	0.5%	Kinney et al, 1995
Toronto, Canada	PM_{10}	40	0.5%	Ozkaynak et al, 1994

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LOCATION AND PERIOD	PARTICULATE MEASURE	MEAN PM$_{10}$ (μg/m^3)	% CHANGE IN MORTALITY FOR EACH 10 μg/m^3 IN PM$_{10}$	REFERENCE
Chicago, IL 1985-90	PM$_{10}$	38	0.6%	Ito et al, 1995
Santiago, Chile	PM$_{10}$	115	0.8%	Ostro et al,1995a
Chicago, IL	PM$_{10}$	37	0.8%	Styer et al, 1995
London, UK	Black Smoke	80	0.3%	Ostro, 1993

Respiratory Mortality

Santa Clara, CA 1980-82, 84-86	Coefficient of Haze	35	3.5%	Fairley, 1990
Philadelphia, PA 1973-80	TSP (2 day mean)	40	3.3%	Schwartz and Dockery, 1992a
Birmingham, AL 1985-88	PM$_{10}$ (3-day mean)	48	1.5%	Schwartz, 1993
Utah Valley, UT 1985-89	PM$_{10}$ (5-day mean)	47	3.7%	Pope et al, 1992
Lyon, France 1985-90	PM$_{13}$	38	0.8%	Zmirou et al, 1996
Barcelona, Spain 1985-91	Black Smoke	42.4	1.0%	Sunyer et al, 1996
Milan, Italy 1980-1989	TSP	139	1.2%	Vigotti et al 1996

Cardiovascular Mortality

Santa Clara, CA 1980-82, 84-86	Coefficient of Haze	35	0.8%	Fairley, 1990
Philadelphia, PA 1973-80	TSP (2 day mean)	40	1.7%	Schwartz and Dockery, 1992a
Birmingham, AL 1985-88	PM$_{10}$ (3-day mean)	48	1.6%	Schwartz, 1993
Utah Valley, UT 1985-89	PM$_{10}$ (5-day mean)	47	1.8%	Pope et al, 1992
Lyon, France 1985-90	PM$_{13}$	38	0.8%	Zmirou et al, 1996
Barcelona, Spain 1985-91	Black Smoke	42.4	1.0%	Sunyer et al, 1996

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Mortality Studies in Australia and New Zealand

The only mortality study in Australia to date has been conducted as part of the HARP studies in NSW (Morgan et al., 1996). This study used mortality data from the Australian Bureau of Statistics for the period 1989 to 1993, and nephelometry data from the NSW EPA air monitoring network. A mean of 59 deaths per day due to all causes was reported, with 28.8 due to cardiovascular disease and 5 due to respiratory disease. Mortality rates were found to increase during the winter months. Nephelometry data was averaged across the entire network to obtain the best available estimate of population exposure.

The results from this study showed that daily deaths from all causes increased by 3 per day for an increase in β_{scatt} from the lowest quartile (10th centile) to the highest quartile (90th centile). This increase corresponded to an estimated increase in PM_{10} of 15 to 40 $\mu g/m^3$. The results of this study are summarised in Table 2 below, and are consistent with overseas experience, namely approximately 1% increase in mortality for every 10 $\mu g/m^3$ increase in fine particle concentration.

TABLE 2
Results of Mortality Study in Sydney (NSW Health Dept).

Cause of Death	Increase in Daily Deaths	Averaging Time
All Causes	2.6%	Today and yesterday
Cardiovascular	2.7%	Today and yesterday
Respiratory	3.4%	Yesterday

On the basis of this study, fine particle air pollution in Sydney accounts for 397 deaths per year out of an annual total of 21500 deaths. Daily mortality was also found to be associated with O_3 and NO_2, but when all pollutants were considered in the same model, the effect of particulates dominated.

A similar mortality study conducted in Brisbane for the period 1987 to 1993, found similar results (Simpson et al., 1997). Significant associations were found for daily mortality and fine particles (measured by nephelometry), NO_2 and O_3. The effects of SO_2 on daily mortality were not significant. When all pollutants were considered in the model, only O_3 and particles remained significant. The associations were more significant for the elderly and for mortality from cardiovascular causes. An increase in fine particle levels corresponding to a 10 $\mu g/m^3$ increase in PM_{10} was associated with an increase in daily mortality of between 1.2 to 1.3%.

Using the overseas estimate of a 1% increase per 10 $\mu g/m^3$ PM_{10} , it has been estimated that respirable particles account for a 2-5% elevation of daily

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mortality rates, approximately 70 premature deaths per year in Perth (Gras, 1996). A similar analysis conducted in Christchurch, New Zealand, has indicated that between 21 and 29 deaths per year may be attributable to PM_{10} levels in that city. This analysis has assumed a threshold value of 30 $\mu g/m^3$, for which there is little (if any) evidence. Total mortality for Christchurch for 1992 was 2519 deaths of which 264 were due to respiratory causes and 721 due to cardiovascular causes. Similar values were obtained for 1993.

These studies have shown that although particle levels in Australia are low they still contribute significantly to premature deaths in sensitive populations. In Christchurch particle levels are significantly higher than those observed in Australian cities and the impact on mortality is estimated to be correspondingly greater.

Conclusions from Mortality Studies

There is a large number of studies which have found significant associations between particulate matter and daily mortality from respiratory and cardiovascular causes. The strength of these findings is the consistency of the results, namely a 1% increase in mortality per 10 $\mu g/m^3$ PM_{10}. These numbers have been found in many studies from various locations worldwide with substantially different climates and socioeconomic environments. It appears that there is no threshold for the effects of particles on mortality, and the most sensitive subpopulations appear to be the elderly and children with existing disease. A recent independent reanalysis of the data from six of these studies by the Health Effects Institute in the USA supports the findings of the original studies. Their results also suggest that the observed associations are not due to some artefact of the modelling. Long-term studies have also shown an association between PM_{10} and $PM_{2.5}$ levels and mortality from lung cancer.

In spite of the consistency of the results, there are still many unanswered questions. Many studies have concluded that the effects of particles cannot be separated from other pollutants, in particular SO_2. The results of studies conducted in the Utah Valley, where very low levels of SO_2 are experienced, indicate that the effects of particulates are observed independently of SO_2 unless there is no threshold for the effects of SO_2. The Sydney study also supports this finding. The question of which particles cause the observed effects is also unknown at this stage. Many different measures of particulate matter have been used in the studies of the association between mortality and particulate matter, and still many find no association. There may be many reasons for these conflicting results including small sample populations, lack of sufficient air monitoring data, statistical modelling and possibly the use of an inappropriate metric for particulate matter. The question as to whether PM_{10} or $PM_{2.5}$ is more important has not been fully resolved at this time due to the small number of studies and lack of data on $PM_{2.5}$. However, positive associations have been observed with both. Studies using Black Smoke as a measure of respirable

particles should be viewed with caution as this may not be a true measure of PM_{10}.

Morbidity Studies

<u>*Hospital Admissions and Emergency Room Visits*</u>

Increased rates of hospitalisation is one of the adverse effects of air pollution. This response was most obvious during notorious air pollution episodes of many years ago, during which increased rates of mortality were also noted. Time-series analysis techniques similar to those used for mortality have been used in several studies to try to deduce quantitative morbidity relationships, for example, for rates of hospital admission and emergency room visits. Particle exposure has been associated with increased hospitalisation for respiratory illness and with other evidence of respiratory morbidity.

Several studies of the effects on respiratory health of air particles have been conducted in the Utah Valley, USA (Pope, 1989; Pope, et al, 1991; Pope, 1991; Ransom and Pope, 1992; Pope and Dockery, 1992). The Utah Valley experiences very high particulate levels due to the presence of a steel mill. During a 12 month period when the steel mill was closed PM_{10} levels decreased considerably. Hospital admissions of children for respiratory illnesses were two to three times higher in the Utah Valley in winter months when the steel mill was open (mean PM_{10} of 87 $\mu g/m^3$, maximum of 365 $\mu g/m^3$) compared with winter months when the local steel mill was closed and PM_{10} concentrations were much lower (mean of 51 $\mu g/m^3$). During months with mean PM_{10} levels greater than or equal to 50 $\mu g/m^3$ average admissions for children and adults increased by 89 and 47%, respectively. Regression analyses also revealed that PM_{10} levels were strongly correlated with hospital admissions. The strongest effects were observed for bronchitis and asthma followed by pneumonia and pleurisy. Daily maximum PM_{10} levels were not as strongly correlated with admissions as were the mean PM_{10} values. The associations observed were particularly strong with monthly lagged variables suggesting that the health effects of particulate pollution are cumulative and that it takes time before they are manifested in inpatient hospital admissions data (Pope, 1989). A further study comparing hospital admissions in 3 counties in Utah confirmed the findings of the previous study (Pope, 1991). In the Utah Valley, hospital admissions in pre-school children for bronchitis and asthma were approximately twice as high when the steel mill was open versus when it was closed. Hospital admissions in Salt Lake and Cache Valleys, which are not affected by particulate air pollution from the steel mill, showed no variation with opening and closure of the steel mill.

Two studies conducted in Minneapolis-St. Paul, Minnesota (Schwartz, 1994c) and Birmingham, Alabama (Schwartz, 1994b) have investigated the effects of daily PM_{10} levels on hospital admissions in the elderly. In the Minneapolis study, PM_{10} levels were strongly associated with hospital admissions for

pneumonia and COPD in persons aged 65 yrs and older. The relative risks associated with a 100 $\mu g/m^3$ increase in PM_{10} levels were 1.17 for pneumonia and 1.57 for COPD. The associations were not sensitive to seasonal and weather variations nor to methods of analysis. Mean PM_{10} levels in Minneapolis-St. Paul during the study period (1986-1989) were 36 $\mu gm/m^3$. The strongest association was observed for same day exposure for pneumonia, and same day and previous day for COPD. In this study O_3 was also associated with hospital admissions for pneumonia, however the effect was much smaller and independent of the effects of PM_{10}. Similar results were obtained in the Birmingham study, with relative risks of 1.19 for pneumonia and 1.27 for COPD observed per 100 $\mu g/m^3$ increase in PM_{10}. Again the results were not sensitive to alternative methods for controlling of weather and seasonal patterns, nor to the exclusion of hot or cold days. Mean PM_{10} levels during the study period (1986-1989) were 45 $\mu g/m^3$. Again the strongest associations were observed for same day exposure. This study found no evidence of a threshold in the relationship between hospital admissions and PM_{10} levels.

A recent study conducted on hospital admissions and PM_{10} data in Cleveland, Ohio (Schwartz et al, 1996) showed statistically significant associations between hospital admissions for respiratory illness and PM_{10} levels in the elderly. The relative risk per 100 $\mu g/m^3$ PM_{10} was 1.12. Associations were also observed for O_3 and SO_2 but these were weaker than that observed for PM_{10}. Mean PM_{10} levels during the study period (1988-90) were 43 $\mu g/m^3$. Similar results were also observed in a study conducted in Detroit Michigan (Schwartz, 1994d). Both PM_{10} and 24 hr ozone levels were associated with hospital admissions for pneumonia and COPD in the elderly for the period 1986-1989. Asthma admissions were not associated with either pollutant. Mean PM_{10} levels were 48 $\mu g/m^3$ during the study period with mean O_3 levels of 21 ppb. The relative risks obtained per 10 $\mu g/m^3$ in PM_{10} were 1.102 for pneumonia and 1.02 for COPD.

PM_{10} levels have also been associated with hospital admissions for cardiovascular disease in Detroit for the period 1986-1989 (Schwartz and Morris, 1995). Hospital admissions for ischemic heart disease and congestive heart failure in persons over the age of 65 yrs were significantly associated with daily levels of PM_{10}. Admissions for heart failure were also associated with daily levels of carbon monoxide. Relative risk ratios obtained in this study for an interquartile range of PM_{10} of 32 $\mu g/m^3$ were 1.018 for ischaemic heart disease and 1.024 for heart failure. Admissions for ischaemic heart disease were not associated with daily levels of SO_2, O_3 or CO. Mean PM_{10} and CO levels during the study period were 48 $\mu g/m^3$ and 2.38 ppm respectively.

Hospital admissions for both cardiac and respiratory have been associated with particulate sulphate levels in 168 Ontario hospitals during the period 1983-1988 (Burnett et al, 1995). A 13 $\mu g/m^3$ increase in sulphate levels (95 th percentile) recorded on the day prior to admission was associated with a 3.7% increase in

respiratory admissions and a 2.8% increase in cardiac admissions and were observed for all age groups. Cardiac admissions were higher in 65 yrs and older age group (3.5%) compared with the under 65 yrs age group (2.5%). Similar results were obtained year round, after controlling for temperature and ozone, suggesting that the observed effects were not due to climatic factors. Mean sulphate levels during the study period were 4.4 μg/m³ with peak levels of 6.3 μg/m³ observed during the summer months. Ozone levels also peaked during the summer months with values of 53 ppb observed. Mean ozone levels during the study period were 36.3 ppb. Sulphur dioxide and nitrogen dioxide were not considered in this analysis.

A study from the UK has indicated that hospital admissions for asthma were associated with levels of Black Smoke and SO_2 in Birmingham for the period 1988-1990 (Walters et al, 1994). Significant associations were found between hospital admissions for respiratory disease lagged by two days, and smoke and SO_2 levels during the winter months. These associations were independent of temperature, pressure and humidity. Stepwise regression including both pollutants showed that smoke and not SO_2 was a significant independent predictor of hospital admissions for both asthma and all respiratory conditions. The mean daily Black Smoke levels during the study period was 12.7 μg/m³ with peak values reaching 188 μg/m³. The results suggest that during the winter a rise of 100 μg/m³ in smoke levels may result in 5 more asthma admissions and 21.5 more acute respiratory admissions each day in Birmingham. Weekly mean smoke and SO_2 levels were also associated with hospital admissions for all respiratory admissions during the autumn and winter. The authors note that the use of black smoke as a measure of particulate air pollution leads to an underestimate of total particulate exposure in this study. A further concern with the results of this study arises from the occurrence of a major influenza epidemic during the winter of 1989/90 (Ponce de Leon and Anderson, 1994) which would have affected admissions for respiratory disease during this period. No attempt was made to control for the effects of this epidemic.

Early studies investigating the association between particulate matter and hospital admissions in London have been reviewed by Lipfert (1993). Several studies utilising data from smog episodes which occurred between 1952 and 1964 showed significant associations between levels of Black Smoke and hospital admissions for respiratory and cardiovascular disorders. In more recent studies (Anderson et al, 1995: Ponce de Leon, 1996) the association was not so clear. Anderson et al., (1995) found an association between air pollution levels and hospital admissions for respiratory disease, asthma, COPD and ischaemic heart disease during an air pollution episode in December, 1991. The strongest associations were observed in the elderly (65 yrs +) for asthma and COPD. No breakdown of pollutants was provided in this study. In a second study (Ponce de Leon, 1996) air pollution and hospital admissions data for the periods 1987-88 and 1991-92 were investigated. No association was found between hospital admissions for respiratory disease and black smoke levels in

any age group. A weak association was found for O_3 and hospital admissions for respiratory disease at all ages. It should be noted that Black Smoke levels were much lower in these later studies compared with the 1950s and 1960s episodes.

A study from Hong Kong (Tseng et al, 1992) has found strong associations between hospital admissions for asthma in the 1-4 yr old age group and TSP. An association was also found for PM_{10} but this was not statistically significant. Mean TSP levels during the study period (1983-1989) were 88 $\mu g/m^3$ while mean PM_{10} levels were 55 $\mu g/m^3$. These authors suggest that the 1-4 yr old age group may be most sensitive to particulate air pollution because of the greater airway surface area to body mass ratio in children in this age group. It was also suggested that this high dose of particulate pollution per body mass could, in a vulnerable airway, cause epithelial damage, epithelial cell dysfunction, initiate inflammation, inception of asthma and subsequent attacks.

During the recent APHEA studies in Europe, associations between hospital admissions and particulate air pollution were examined in Paris (Dab et al., 1996), Helsinki (Pönkä et al, 1996), and Milan (Vigotti et al., 1996). The Paris study (Dab et al, 1996) found that levels of both PM_{13} and Black Smoke were associated with hospital admissions for respiratory diseases when levels exceeded 120 $\mu g/m^3$. The strongest association was observed with PM_{13} with a 4.5% increase in hospital admissions with same day exposure. The results from the Helsinki study showed no association between TSP levels and hospital admissions for asthma (Pönkä et al, 1996) for the period 1987-89. These results however were thought to be inconclusive due to problems with the model used. A previous study in Helsinki (Pönkä, 1991) showed strong associations between hospital admissions for asthma and TSP levels between 1987-1989. Mean TSP levels were 76.3 $\mu g/m^3$ during the study period. Highly significant correlations were also found between hospital attendances for asthma and SO_2, NO, NO_2 and CO. The 15-64 yr old age group appeared to show the strongest association followed by the over 65 yr age group. Children under 14 appeared to be the least sensitive. The conflicting results from the two Helsinki studies, which were conducted over the same period, may be due to a number of variables. The main differences were in the model used and the population sample size. In the earlier study there were roughly double the number of hospital admissions for asthma. The reason for this discrepancy is not clear from the papers. The smaller sample size may have a large effect on the power of the statistical model in being able to identify significant associations. The other difference, namely the model used for the analysis, may have an even greater effect and highlights the need for caution in the choice of model used in epidemiological studies such as these.

In the study from Milan (Vigotti, 1996) positive associations were found for hospital admissions for respiratory causes and daily TSP and SO_2 levels. The relative risks were similar for both pollutants. Mean TSP levels during the study period (1980-89) were 139 $\mu g/m^3$. An increase of 5% per 100 $\mu g/m^3$ in

TSP was observed in hospital admissions for respiratory disease. No effect was seen within different age groups, however stronger effects were observed in the 15-64 yr age group during the warmer months. There was no evidence of any interaction with SO_2 levels.

PM_{10} levels in Montreal have been found to be strongly associated with hospital admissions for asthma (Delfino et al., 1994) during the period 1984-88. Asthma admissions during the spring and summer months increased by 2.7% per 12 $\mu g/m^3$ increase in PM_{10} levels 3 days prior to the admission day. This study was conducted during the warm months and mean PM_{10} levels were 29.5 $\mu g/m^3$ and maximum of 85 $\mu g/m^3$. Generally mean respiratory admission levels were 9% higher during pollution episodes than during non-episodes. This study also found an association between sulphate levels and hospital admissions for respiratory illness.

Hospital admissions during a smog episode in West Germany (Wichmann et al, 1989) were found to increase by 15% in the polluted area. The increase was more pronounced for cardiovascular disease (19%) than for respiratory diseases (7%). TSP levels during this period reached as high as 600 μm^3 with 24 hr average levels of 440 $\mu g/m^3$.

In the review by Dockery and Pope (1994), hospital admissions and emergency department visits increased approximately 1% per 10 $\mu g/m^3$ PM_{10} for all respiratory complaints, and 2 to 3% for asthma. Exacerbation of asthma increased by about 3%, as did lower respiratory symptoms. Small decreases in lung function, approximately 0.1%, have also been observed. This review suggested that the morbidity measures were coherent with the mortality studies showing quantitatively similar adverse effects of acute exposures to particulate air pollution.

Significant associations between emergency room visits for asthma and PM_{10} levels were observed in Seattle, Washington for the period 1989-90 (Schwartz et al., 1993). The relative risk per 30 $\mu g/m^3$ of PM_{10} was 1.12. The mean of the previous 4 days PM_{10} gave the strongest association. Mean PM_{10} concentrations during the study period were 29.6 $\mu g/m^3$ with a maximum level of 103 $\mu g/m^3$. No noticeable association was found between emergency room visits for asthma and PM_{10} in the elderly. A clear dose-dependent increase was observed and there was no evidence of a threshold.

Total emergency room visits were associated with SO_2 and TSP levels in Steubenville, Ohio, for the spring and autumn months in 1974 to 1977 (Samet et al, 1981). A 3% increase in emergency room visits for respiratory disease was observed per 100 $\mu g/m^3$ increase in TSP levels. Maximum levels of TSP in this study reached 696 $\mu g/m^3$.

Black Smoke levels were found to be associated with emergency room visits for COPD in Barcelona, Spain for the period 1985-89 (Sunyer et al., (1993). The association was stronger in the winter than in the summer with a 6% increase in

emergency room visits per 25 μg/m^3 Black Smoke observed. The weaker association observed during the summer may be due to fact that Black Smoke is a poorer indicator of respirable particulate matter during the summer months (Horvath, 1996). In an earlier study on emergency room admissions for COPD in Barcelona during 1985-1986, increases in Black Smoke levels of 100 μg/m^3 led to an increase in of one person in daily admissions (Sunyer et al, 1991). Carbon monoxide and sulphur dioxide levels were also associated with daily COPD admissions. Although this association was weak, it was statistically significant. Black Smoke levels ranged between 39 and 310 μg/m^3 with a mean value of 73 μg/m^3.

A study of asthmatic children in Oporto, Portugal, during the period 1983-1987, found no association between levels of particulate matter, measured as Black Smoke, and frequency of hospital admissions or emergency room visits for asthmatic attacks (Queirós et al, 1990). Mean Black Smoke levels during the study period were 21.7 μg/m^3 . Long-term exposure to SO$_2$ (greater than 1 month) were found to have a significant positive association with an increase in asthma attacks.

A summary of the results from the studies on hospital admissions and emergency room studies is presented in Table 3 below:

TABLE 3
Summary of Particle and Hospital Admissions and Emergency Room Studies

LOCATION AND PERIOD	PARTICULATE MEASURE	MEAN PM$_{10}$ LEVEL μg/m^3	% CHANGE IN HOSPITAL ADMISSIONS FOR EACH 10 μg/M^3 PM$_{10}$	REFERENCE
Birmingham, Alabama 1986-1989	PM$_{10}$	45	pneumonia in the elderly 1.9% COPD in the elderly 2.7%	Schwartz (1994)
Barcelona, Spain 1985-1989 Ages 14 yrs and older	Black Smoke		3% COPD winter 1% COPD summer	Sunyer et al, (1991)
Montreal, Canada 1984-1988	PM$_{10}$	45.7	asthma 2.3%	Delfino et al (1994)
Seattle, Washington 1989-1990	PM$_{10}$	29.6	Emergency Room Visits for asthma 4%	Schwartz et al (1993)
Cleveland, Ohio	PM$_{10}$	43	Elderly 1.2%	Schwartz et al (1996)

LOCATION AND PERIOD	PARTICULATE MEASURE	MEAN PM$_{10}$ LEVEL μg/m³	% CHANGE IN HOSPITAL ADMISSIONS FOR EACH 10 μg/M³ PM$_{10}$	REFERENCE
Paris, France	PM$_{13}$	50.8	0.45% all respiratory	
	Black Smoke	31.9	0.43% asthma 0.41% all respiratory	
Milan, Italy	TSP	139	all respiratory 0.5%	
Minneapolis-St Paul, Minnesota 1986-1989	PM$_{10}$	36	Elderly 1.7% pneumonia 5.7% COPD	Schwartz (1994)
Toronto, Canada July and August 1986-1988	PM$_{10}$	35	1.8% respiratory	Thurston et al, 1994
Detroit, Michigan 1986-89 Elderly	PM$_{10}$	48	2.2% COPD 1.2% pneumonia	Schwartz, 1994(?)

Hospital Admission and Emergency Room Visits Studies in Australia and New Zealand

A study conducted in Melbourne investigated the association between asthma attendances at the Emergency Department of the Royal Children's Hospital and nephelometry data from the EPA's air monitoring network (Rennick and Jarman, 1992) during smog days. Peak asthma attendances occurred during the winter months. A highly statistically significant association was found between asthma attendances and days with high levels of fine particulates (reported as API). A lag effect was noted with associations observed up to 2 days after the occurrence of a smog day. Asthma attendances were also associated with API levels up to 2 days prior to the smog day. No association was found between asthma attendances and ozone levels during summer smog periods.

Hospital admissions for COPD and heart disease in Sydney have found to be associated with daily maximum 1 hour fine particle levels as measured by nephelometry (Morgan et al., 1996) for the period 1990-1994. Increases of 3% for COPD and 2.5% for heart disease have been found for an increase in fine particle levels from the lowest to the highest quartiles, corresponding to a PM$_{10}$ range of 15 to 40 μg/m³. Two further studies conducted as part of the HARP program found no association between particulate levels in Sydney and asthma attendances at hospitals (Helby, 1996; Corbett et al., 1996). Corbett et al, investigated hospital admissions and emergency room attendances for asthma during the NSW bushfires which occurred in 1994. During the 8 day period of

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the fires, PM_{10} levels were consistently high and peaked at 250 $\mu g/m^3$. No increase was observed in hospital attendances or emergency room attendances during the bushfire period, but this may have been due to the short duration of the event which may not allow for small changes to be detected. Helby et al, investigated emergency room attendances for asthma in south west Sydney between 1990 and 1993. Again no correlation was found between airborne particles and asthma attendances, although a weak, non-significant, association was found with NO_2.

A large study has been conducted in Launceston and the Upper Tamar Valley, Tasmania, during 1992 and 1993 to assess the impact of air pollution in the region on respiratory health (Lyons et al, 1996). Launceston experiences high particulate pollution levels during the winter months due to a combination of meteorology and woodsmoke from domestic heating. Hospital admissions data for asthma, bronchitis and COPD were assessed together with two control non-respiratory conditions - appendicitis and myocardial infarction. PM_{10} measurements were collected and averaged over 5 sites in the Launceston area. Hospital admissions for respiratory disease were found to be higher in winter and exhibited a general upward trend between 1991 and 1993. Air pollution levels are also higher during the winter months. Statistical analysis showed no correlation between the hospital admissions data and PM_{10} levels in Launceston. Similar results were found for emergency room attendances. This finding needs to be interpreted carefully due to the small amount of air monitoring data (PM_{10} was collected on an "every-6-day- cycle" for a 3 year period) and the small study population. Further analysis is continuing.

Studies are currently underway in Brisbane to investigate the association between hospital admissions and air pollution (Simpson, 1996).

Estimates of hospital admissions due to airborne particles have been conducted in Christchurch, New Zealand (Foster, 1996). Using the average values for hospital admissions per 10 $\mu g/m^3$ increase in PM_{10} , as determined by Dockery et al., (1994), up to 11 hospitalisations for respiratory disease, 17 hospitalisations for cardiopulmonary disease and 17 hospitalisations for asthma may be associated with PM_{10} levels in Christchurch per year.

Conclusions from Studies on Hospital Admissions and Emergency Room Attendances

As with the mortality studies, hospital admissions and emergency room visits for respiratory disease have been associated with levels of particulate matter. Increases of approximately 1% per 10 $\mu g/m^3$ increase in PM_{10} have been observed for all respiratory illnesses and 2-3% for asthma. The effects of particulate matter appear to be cumulative as indicated by observed lag periods for hospital attendances and sensitive groups appear to be children and the elderly with existing disease. No threshold has been observed for these effects.

Results of limited studies in Australia have found similar results to the overseas studies.

Respiratory Illness and Lung Function Studies

Respiratory illness and the factors determining its occurrence and severity are important public health concerns. This is due to the potential widespread potential for exposure to airborne particles and because the occurrence of respiratory illness is common (Samet et al, 1983; Samet and Utell, 1990). Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage (Glezen 1989; Samet et al, 1983; Gold et al, 1989).

Studies investigating the effects of particulate matter on respiratory health have generally used several different standard respiratory questionnaires that evaluate health status by asking questions about each person's respiratory disease and symptom experience daily, weekly or over a longer time period. The reported symptoms and diseases characterise respiratory morbidity in the cohorts studied. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader categories such as upper and lower respiratory illnesses. Asthma is characterised by reversible airway obstruction, airway inflammation and increased airway responsiveness to stimuli (National Institutes of Health, 1991). Asthma patients develop clinical symptoms such as wheezing and dyspnoea (difficulty in breathing) after exposure to allergens, environmental irritants, viral infections, cold air or exercise (US EPA, 1995). Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms associated with decreased levels of various measures of forced expiratory volume (FEV). Chronic bronchitis in adults is defined as a clinical disorder characterised by excessive mucous secretion in the bronchial tube with an associated chronic productive cough on most days for a minimum of 3 months of the year for not less than 2 years (American Thoracic Society, 1962). Symptoms and findings in children with physician-diagnosed chronic bronchitis commonly include recurrent respiratory infections and wheezing, with chronic phlegm production and chronic cough being less prevalent (Burrows and Lebowitz, 1975).

Viral respiratory illnesses can be subdivided by the predominant anatomic site of involvement in the respiratory tract: rhinitis (the common cold), pharyngitis, laryngitis, croup, tracheobronchitis, bronchiolitis, and pneumonia. The common cold is the leading acute upper respiratory illness reported. In most adults and older children signs and symptoms of the common cold are marked by a dry, scratchy sore throat. Sneezing, irritated or runny nose are subsequent symptoms. Typically, symptoms and responses on respiratory questionnaires for upper respiratory illness include throat irritation, acute cough, cough with phlegm, wheeze, runny nose, breathing difficulty, fever and earache.

Lower respiratory illnesses are generally classified into four categories: croup, tracheobronchitis, bronchiolitis and pneumonia (Glezen and Denny, 1973; Wright et al, 1989). The most common signs and symptoms of lower respiratory illness in children are wet cough (85%), wheeze (77%), Tachypnoea (rapid breathing, 48%), fever (54%), and croupy cough (38%) (Wright et al, 1989). Infectious agents such as respiratory syncytial virus is particularly likely to cause lower respiratory symptoms during the first two years of life. It has been reported that respiratory illnesses in childhood are important determinants for the future risk of chronic respiratory symptoms and disease in adult life (Samet et al, 1983; Glezen ,1989).

Several studies have been conducted to ascertain the effect of airborne particulate matter on respiratory health. Studies of respiratory illness incidence in children have shown associations with particulate concentrations at current ambient levels. A study conducted in the Utah Valley during the winter of 1990-91 (Pope and Dockery, 1992) found strong associations between respiratory symptoms and lung function with daily PM_{10} levels. Participants in the study included symptomatic and asymptomatic school children . Large associations between PM_{10} levels and the incidence of respiratory symptoms, especially cough, were observed for both samples, but more for the symptomatic group. Immediate and delayed effects were observed. Respiratory symptoms and peak expiratory flow (PEF) changes were more closely associated with 5-day moving-average PM_{10} levels than with concurrent days. PEF values were lower and reporting of symptoms was higher when PM_{10} levels were higher. For the symptomatic sample, those reporting upper respiratory symptoms, lower respiratory symptoms and cough were approximately 57, 82 and 100% higher, respectively, during days with pollution levels in the highest quartile versus days in the lowest quartile. Mean 24 hr PM_{10} concentrations ranged from 7 to 251 $\mu g/m^3$ during the study period. The participants in this study were required to fill out daily health symptom diaries which involved reporting of symptoms such as trouble breathing; runny or stuffy nose; wet cough; dry cough; wheezing; fever; rash; burning; aching or red eyes and upset stomach. In addition peak flow readings were performed three times before going to bed. The impact of particulate air pollution on lung function and symptoms of respiratory disease appears to be transient, however the impact on the risk of developing respiratory disease as adults is unclear.

An earlier study conducted in the Utah Valley (Pope et al., 1991) examined the association between respiratory symptoms, lung function and asthma for the winter period of 1989-1990. Two groups of participants were included in this study: a school aged group, fourth and fifth grades, and a sample of patients with asthma aged 8 to 72 yrs. Participants were required to fill out daily diaries reporting the following symptoms: trouble breathing; runny or stuffy nose; wet cough; dry cough; wheezing; fever; rash; burning; aching or red eyes and upset stomach. They also reported if they stayed home for a day; saw a doctor or nurse; were hospitalised; took asthma medication on a given day; took extra

asthma medication that day; or were out of town overnight. The results of this study showed statistically significant associations between reduction in lung function and PM_{10} levels which were stronger in the school based sample. Elevated levels of PM_{10} were also associated with increases in reported symptoms of respiratory disease and use of asthma medication in the school based sample. In the patient based sample, no associations between PM_{10} pollution and reported symptoms of respiratory disease were observed. A statistically significant positive association between PM_{10} pollution and reported use of asthma medication was observed. The probability of the use of extra asthma medication was 6.2 times higher when 24 hr PM_{10} levels were at the highest level versus the lowest. PM_{10} levels ranged between 11 and 195 $\mu g/m^3$ during the study period with a mean level of 42 $\mu g/m^3$ and there was little or no strong acidity present. Daily peak flow measurements suggest that the deficit in pulmonary function in response to particulate pollution episodes can be seen immediately but continue to accumulate for several days.

A study conducted in Seattle during two winters (1988-89, 1989-90) has shown that increased levels of fine particles (measured via nephelometry) were associated with a decline in lung function in asthmatic children (Koenig et al, 1993). The main source of particulates in the study area during the winter months is wood smoke from domestic heating. Forced expiratory volume (FEV_1) and forced vital capacity (FVC) in asthmatic children dropped an average of 34 and 37 ml respectively for each 10^{-4} m^{-1} increase in β_{sp}. This increase in β_{sp} level corresponded to an increase in $PM_{2.5}$ of 20 $\mu g/m^3$. The results obtained in this study for reductions in FVC are more pronounced than those observed by Dockery et al (1982) for children in Steubenville, Ohio. In the Dockery study TSP was used as a measure of airborne particulates and associations were examined immediately before and after high pollution episodes. $FEV_{0.75}$ was reported to decline following these episodes and remained depressed for a period up to 2 weeks. FVC was 2% lower following each of the episodes and again remained depressed for 1 to 2 weeks. Koenig et al (1993) suggest that these differences may be due to an increased sensitivity to airborne irritants in children with asthma or may suggest that fine particulate matter is more irritating than TSP. It is also possible that wood smoke, due to its respirable size fraction and composition, may be more irritating than TSP from other sources.

Ware et al (1986) as part of the six cities study investigated the effects of TSP, the sulphate component of TSP and SO_2 on the respiratory health of preadolescent children. The study enrolled 10,106 children who were followed up over a three year period. Across the six cities, frequency of cough was significantly associated with the average 24 hr mean concentrations of all three air pollutants . Rates of bronchitis and lower respiratory illnesses were significantly associated with TSP levels. Within each of the cities however, air pollutant concentrations were not significantly associated with symptoms or respiratory illness. Pulmonary function parameters, FEV_1 and FVC, were not

found to be associated with any measure of air pollution. Dockery et al., (1989) carried out a further investigation into the effects of particulate air pollution on respiratory health of children participating in the six cities study. This study used air monitoring data for TSP, PM_{15}, $PM_{2.5}$, fine particulate sulphate, SO_2, O_3 and NO_2 and results from a questionnaire on the respiratory symptoms and illnesses of children during the 1980-81 school year. The study found that after controlling for variables such as sex, age, indicators of parental education, maternal smoking, and use of a gas stove in the home, significant associations were found between rates of chronic cough, bronchitis, and chest illness with all measures of particulate pollution (ie., TSP, PM_{15}, $PM_{2.5}$, and particulate sulphate). Positive associations were also found with NO_2 and O_3, however these were weaker than those observed for particulates. No associations were found for any pollutant with asthma, persistent wheeze, hay fever, non respiratory illness, nor with any measure of pulmonary function. Children with a history of wheeze or asthma had a much higher prevalence of respiratory symptoms, and there was some evidence that the association between air pollutant concentrations and symptom rates was stronger among these children. The authors concluded that the lack of association between pollutant concentrations and measures of pulmonary function suggests that the observed increased rates of illness are not associated with permanent loss of pulmonary function, at least during preadolescent years.

During an air pollution episode in the Netherlands in February 1991, 24 hr average PM_{10} levels reached 174 $\mu g/m^3$ and SO_2 levels 100 $\mu g/m^3$ (Hoek et al, 1993). During this period respiratory symptoms in children aged 7-12 yrs of age were recorded in a diary. Symptoms included throat irritation, cough, cough with phlegm, wheeze, runny nose, aching throat, shortness of breath, chest tightness, eye irritation and sneezing. Some non respiratory symptoms, such as earache, nausea, and fever, were also included. The results of this study showed no association between respiratory symptoms and any air pollutant. Declines observed in pulmonary function were associated with temperature.

Significant associations were found between PM_{10} levels and PEF in children with a history of asthma in a study from Eastern Europe (Peters et al., 1996). Sulphates were the strongest predictor for decreases in PEF when all other pollutants were included in the model. A strong positive association was found for respiratory symptoms in children and the 5-day mean of PM_{10} levels. A 6.1% increase in symptoms was associated with a 48 $\mu g/m^3$ increase in PM_{10}. Effects on children were generally larger and more consistent than for adults. Only a 5-day mean of TSP was associated with PEF in adults. The 5-day mean of PM_{10} levels was associated with respiratory symptoms in adults. A 14.6% increase in symptoms was associated with a 48 $\mu g/m^3$ increase in PM_{10}.

A study conducted in Liepzig, East Germany, investigated the effects of air pollution on the respiratory health of school children (von Mutius et al, 1995).

Upper respiratory symptoms such as runny nose, cough or hoarseness, were found to be associated with daily levels of SO_2, NO_2 and particulate matter (size unspecified) during the winter months. Daily maximum levels of PM ranged between 53 and 1040 $\mu g/m^3$. The association with PM was only observed at very high levels. During the summer months the only association was found for NO_2. Emissions during the high pollution winter months were from industry as well as domestic coal burning for heating. During the summer when PM levels were much lower, the emissions were mainly from industrial sources.

Braun-Fahrländer et al, (1992) studied daily respiratory disease symptoms in preschool children in 4 areas of Switzerland. A sample of 840 children was chosen from Basel and Zurich. Parents recorded daily symptoms including cough without runny nose, breathing difficulty, and fever with earache and sore throat. Ambient levels of TSP, NO_2 and SO_2 were measured by city monitors. In addition, passive samplers inside and outside the home measured NO_2 concentrations. TSP was found to be significantly associated with incidence of cough and upper respiratory symptoms. The relative risks were 1.16 and 1.12, respectively, for a 20 $\mu g/m^3$ increase in TSP. No association was found between NO_2, SO_2 and O_3 levels and incidence of cough, however, NO_2 was found to be associated with symptoms of upper respiratory disease (relative risk 1.23 per 20 $\mu g/m^3$ increase). Only outdoor levels of NO_2 were associated: NO_2 monitored indoors was highly insignificant. No association was found between pollution and the incidence of breathing difficulty or any symptom. TSP and NO_2 outdoor were also significant predictors of the duration of any respiratory episode. The strongest associations were found for previous day exposure. TSP levels during the study period ranged from 30 to 117 $\mu g/m^3$.

Ransom and Pope (1992) examined the relationship between elementary school absences and PM_{10} pollution in the Utah Valley between 1985 and 1990. PM_{10} concentrations during this period averaged 50 $\mu g/m^3$ with a maximum value of 365 $\mu g/m^3$. After controlling for temperature, snowfall, day of the week, month of school year and days preceding and following holidays and long weekends, a significant association was found between school absenteeism and PM_{10} levels. A 100 $\mu g/m^3$ increase in a 28 day moving average PM_{10} levels was associated with a 2% increase in school absenteeism. PM_{10} effects persisted for up to 3-4 weeks.

Between 1976 and 1980, the National Health and Nutrition Examination Survey (NHANES II) was conducted with 20,322 participants between the ages of 6 months and 74 yrs. Data were collected for the health status of participants and air monitoring data from multiple locations around the US. A study conducted by Schwartz (1989) used the data from this study to investigate the association between lung function and chronic exposure to air pollution. After controlling for age, height, race, sex, body mass, cigarette smoking and respiratory symptoms, forced vital capacity (FVC) and forced expiratory volume (FEV_1)

showed strong statistically significant associations with TSP, NO_2 and O_3. Strongest associations were observed for NO_2 and O_3 No association was found for SO_2. A second study utilising the data from NHANES I, which was conducted at 90 locations throughout the US, again found strong significant associations between TSP levels, FEV_1 and FVC (Chestnut et al, 1991). The results from this study indicated that a 34 $\mu g/m^3$ increase in TSP levels was associated with an average decrease in FVC of 2.25%. The results also suggested that a threshold exists for TSP below which the relationship between lung function and TSP ceases to exist. This threshold occurs at approximately 60 $\mu g/m^3$. A further study utilising the data from the NHANES I study (Schwartz, 1993) found strong associations between annual average levels of TSP and an increased risk of chronic bronchitis and of a respiratory diagnosis by a physician. The relative risks per 10 $\mu g/m^3$ increase in TSP were 1.07 for chronic bronchitis and 1.06 for respiratory diagnosis. When the analysis was restricted to never smokers, the associations remained, with a slight increase in the relative risk with airborne particles. TSP was not associated with the prevalence of asthma or dyspnoea (difficulty in breathing).

Acute effects of PM_{10} pollution on pulmonary function has been investigated by Pope and Kanner (1993). The study population consisted of smokers who suffered from mild to moderate chronic obstructive pulmonary disease (COPD). Significant associations were found between changes in pulmonary function and PM_{10}. On average , an increase in PM_{10} equal to 100 $\mu g/m^3$ was associated with a decrease in FEV_1 of 2%. Associations between PM_{10} and FVC were not statistically significant. No analysis was conducted for SO_2 or O_3.

Xu et al (1991) examined the effects of air pollution on adult pulmonary function in Beijing, China. Respiratory diseases are the second leading cause of death in the overall population of China and air pollution is believed to be one of the most important risk factors (Xu et al, 1991; Tao et al, 1992). Higher levels of air pollutants have been found in northern cities compared with southern cities and levels are higher during the winter than the summer. Daily mean concentrations of TSP in 60 cities in China were as high as 660 gg/m^3 (Xu et al, 1991). Indoor air pollution caused by cooking and heating with coal is considered a major contributor to the incidence of respiratory disease (Tao et al, 1992). Xu et al found associations between both indoor and outdoor levels of TSP and SO_2 and reductions in FEV_1 and FVC. The results suggested that subjects who did not use coal for heating, and therefore had exposure to lower levels of indoor pollution, were more sensitive to the effects of outdoor particulate levels. Tao et al (1992) found that indoor levels of PM_{10} were more closely associated with both mortality and morbidity of COPD than ambient levels in Shanghai. Ambient PM_{10} levels ranged between 60 and 309 $\mu g/m^3$ in the region during the study period. No association was found between ambient PM_{10} levels and mortality, however indoor levels were significantly associated especially in households that used coal for heating. Symptoms of COPD were found to be associated with both indoor and outdoor levels but more strongly with indoor. When all outcomes were regressed in the same model no

association was found with outdoor levels. The conclusion of this study was that indoor levels of particulates, especially in households that use coal for heating, was far more important for the prevalence of COPD in Shanghai residents than ambient particulate levels.

A further study by Xu and Wang (1993) investigated the association of indoor and outdoor particulate levels with chronic respiratory illness in Beijing. Respiratory symptoms of 3,606 subjects between the ages of 40 and 69 yrs were recorded over a 2 month period. These symptoms included chronic cough, chronic phlegm, bouts of cough and phlegm, shortness of breath, wheeze and wheeze with shortness of breath. Total particulate exposure, represented by the sum of indoor and outdoor particulate levels, was significantly associated with increased prevalence of all the six symptoms. A similar trend was noted for bronchitis, however, no association was found between asthma and exposure to particulates. The association was stronger with residents of houses who used coal for heating and cooking. Particle levels were significantly higher in these households. The mean ambient particle level, as TSP, during the study period was 230 $\mu g/m^3$ for residential areas whilst the indoor level was 90 $\mu g/m^3$.

The effect of long-term exposure to airborne particulate matter on the symptoms and development of COPD in non-smoking Seventh-Day Adventists in California has been investigated (Euler et al, 1987; Abbey et al, 1995). Seventh-Day Adventists form a sub-population whose response to air pollution may differ from the general population due to their abstinence from cigarette smoking, and alcohol. In addition they have very low exposure to in-home passive smoke. In the study by Euler et al, (1987), 7,445 participants were asked to complete respiratory symptom questionnaires. Of this population, 25% were exposed to TSP levels greater than 200 gg/m^3 for at least 750 hours per year. Associations were found between symptoms of COPD and this exposure to TSP. The relative risk was 1.22. The results indicated that about one quarter of the study population experience frequent exposure to TSP levels high enough during an 11 yr period to demonstrate an association with a 22-32% increase in risk toward developing COPD symptoms. An association was also found for SO_2 for exposures of 4 pphm for 500 hours per year. An 18% increase was observed for exposures over an 11 yr period. Only 13.3% of the population are exposed to these levels compared to 25% for TSP. In the study by Abbey et al., (1995), significant associations were found between airborne particulate matter and respiratory disease. Particulate matter was measured as TSP, PM_{10}, $PM_{2.5}$ and visibility. The results of this study need to be interpreted with caution as only TSP was measured directly: all other particulate measures were estimated. Strong associations were found between long-term exposure to TSP levels above 200 $\mu g/m^3$ and the development of COPD, chronic bronchitis, and asthma. The incidence of all malignant cancers in women, and respiratory cancer in men and women, were also highly associated with exposure to TSP at these levels. The relative risks associated with exposure were 1.36, 1.33 and 1.74 for the

development of COPD, chronic bronchitis and asthma, and 1.37 and 1.72 for incidence of all malignant cancers in women and respiratory cancers in men and women, respexively. Estimates of other particulate measures also showed strong associations. Ozone was found to have strong associations with all health outcomes. The highest relative risks were for development of asthma (1.35) and incidence of respiratory cancer (2.25). No association was found for SO_2 and any health outcome.

Several studies have investigated the effects of airborne particles on asthmatics. Ostro et al., (1991) found strong associations between acidity of the aerosol and symptoms of asthma including moderate or severe cough and shortness of breath in a group of 207 asthmatics during the winter of 1987-88 in Denver, Colorado. Cough was also found to be associated with $PM_{2.5}$ and shortness of breath with sulphates. The conclusion from this study was that although $PM_{2.5}$ and sulphates were associated with symptoms of asthma, airborne acidity appeared to be the major factor. Mean pollutant levels during this study were H^+ 10.07 neq/m³, 21.97 µg/m³ $PM_{2.5}$, and 2.11 µg/m³ sulphates.

In a study from Sweden (Forsberg et al, 1993) daily variations in Black Smoke levels were associated with the risk of developing shortness of breath but not with cough or phlegm production in a group of 31 asthmatics. Symptoms were recorded in a daily diary during the months of March and April, a period with low pollen levels. Mean daily Black Smoke levels during the study period were 7.1 µg/m³. Sulphur dioxide and nitrogen dioxide levels were not associated with reported symptom of asthma.

Another measure of the acute impact of air pollution on health is the restricted activity days. Ostro et al., (1989) investigated the correlation between fine particles, $PM_{2.5}$, and respiratory-related restricted activity days (RRAD) and minor restricted activity days (MRAD). RRAD were defined as any day on which a person was required to alter his or her normal activity and an acute respiratory condition was reported. It includes work loss or bed disability as well as more minor conditions and as such is a good indicator of respiratory morbidity. A MRAD is a restricted activity day that does not result in either work loss or bed disability and therefore involves more minor conditions and reductions in activity. The sample population were working adults aged between 18 and 65 yrs and was taken from the Health Interview Study conducted on 50,000 households across the US for the period 1976-81. The results of this study indicated that there is a significant consistent relationship between fine particles and RRAD. A 1µg/m³ change in fine particle levels was associated with a 1.58% increase in RRAD or an excess of 4800 RRAD per 100,000. No association was found for O_3. The association between MRAD and fine particles was weaker than that observed with RRAD. For MRAD, a 1 µg/m³ increase in fine particle levels was associated with a 0.82% increase in MRAD or an excess of 6400 MRAD per 100,000. Weak associations were observed for O_3 and MRAD.

The impact of exhaust emissions from busy roadways on the respiratory health of individuals living in close proximity to those roadways has long been suspected, however useful objective data has been lacking. In a report recently to hand (Brunekreef et al 1997), the impact of traffic-related air pollution on the respiratory health of children living in several separate locations in Holland was assessed. These motorways carried between 80,000 and 152,000 vehicles daily. Some 1200 children were assessed, and many lived within 1000 metres of the roadways. Lung function changes were found to be related to truck traffic density , but less so with automobile traffic density. In addition, the association was stronger if the children lived within 300 metres of the motorways concerned. There appeared to be a linear relationship between reduction in lung function in children living within 300 metres of the motorway and the truck traffic density on weekdays. As a separate part of the study, lung function was also measured in local schools, and associated with Black Smoke, used in this instance as a surrogate for diesel exhaust particles. The associations were stronger in girls than in boys, for reasons that are not clear at this time. The authors concluded that exposure to traffic-related air pollution, in particular to diesel exhaust particles, may lead to reduced lung function in children living near major motorways.

A summary of the studies on particulate matter and respiratory symptoms and lung function is shown in Table 4 overleaf:

TABLE 4
Summary of Studies of Particulate Matter and Respiratory Symptoms and Lung Function

LOCATION, PERIOD AND SAMPLE POPULATION	PARTICULATE MEASURE	% CHANGE IN RESPIRATORY SYMPTOMS FOR EACH 10 µg/m³ CHANGE IN PM_{10}	REFERENCE
Lower Respiratory Symptoms			
Utah Valley, UT, Winter 1989-90	PM_{10} daily mean		Pope et al (1991)
Children		5.1%	
Asthmatics		0.2%	
Utah Valley, UT Winter 1990-91	PM_{10} daily mean		Pope and Dockery (1992)
Symptomatic Children		4.8%	
Asymptomatic Children		2.4%	
Wageningen, Netherlands Winter 1990-91 School Children	PM_{10} daily mean	1.2%	Hoek and Brunekreef (1993a)
Four Dutch Cities Winter 1987-90 School Children	PM_{10} previous day	1.5%	Hoek and Brunekreef (1993b)
Southern California, Winter 1978-79	COH daily mean		Ostro et al (1993)
Non-smoking adults		5.9%	
Upper Respiratory Symptoms			
Utah Valley, UT, Winter 1989-90	PM_{10} daily mean		Pope et al (1991)
Children		3.7%	
Asthmatics		-0.2%	
Utah Valley, UT Winter 1990-91	PM_{10} daily mean		Pope and Dockery (1992)
Symptomatic Children		3.7%	
Asymptomatic Children		-0.2%	
Wageningen, Netherlands Winter 1990-91 School Children	PM_{10} daily mean	2.6%	Hoek and Brunekreef (1993a)
Four Dutch Cities Winter 1987-90 School Children	PM_{10} previous day	-0.2%	Hoek and Brunekreef (1993b)

LOCATION, PERIOD AND SAMPLE POPULATION	PARTICULATE MEASURE	% CHANGE IN RESPIRATORY SYMPTOMS FOR EACH 10 μg/m³ CHANGE IN PM_{10}	REFERENCE
Southern California, Winter 1978-79 Non-smoking adults	COH daily mean		Ostro et al (1993)
		2.7%	
Cough			
Utah Valley, UT Winter 1990-91 Symptomatic Children Asymptomatic Children	PM_{10} daily mean	5.2% 3.4%	Pope and Dockery (1992)
Four Dutch Cities Winter 1987-90 School Children	PM_{10} previous day	1.3%	Hoek and Brunekreef (1993b)
Two Dutch Cities Winter 1990-91	PM_{10} previous day	0.1%	Roemer et al (1993)
Two Swiss Cities	Previous Day TSP	8.6%	Braun-Farhlander et al (1992)
Uniontown, PA Summer 1990	Daytime mean $PM_{2.5}$	28.1%	Neas et al (1992)

Respiratory Symptoms and Lung Function Studies in Australia and New Zealand

A diary study was conducted in Brisbane on behalf of the Asthma Foundation in Queensland, to investigate the association of bioaerosols and air pollution on the incidence of asthma (Simpson et al, 1995). Between 100 and 120 subjects with asthma kept daily diaries of symptoms, lung function (PEF) and medication use for the period April 1994 to September 1995. Hospital attendance data was also collected during this period. Preliminary results have shown a significant association during the spring between the incidence of asthma severity with elevated levels of particulates and pollen. Biomass burning during this period is a major source of respirable particles. No association was found between asthma and particulates during the winter months when particle levels are at the lowest levels. Weak, but significant, effects were noted during the autumn period. Particulates were measured as PM_{10} and β_{sp} (light scattering coefficient from nephelometry data) and the strongest association between asthma severity and particulate air pollution appeared to be with PM_{10}: β_{sp} was correlated at only one site during 1994. Time series analysis has shown that PM_{10} at both Brisbane South and Ipswich

and β_{sp} at Ipswich are associated with decreases in PEF. Studies are continuing into the effects of air pollution and bioaerosols on asthma severity in Brisbane (Simpson, 1996).

Two studies conducted as part of the HARP program in NSW have investigated the influence of air pollution on the respiratory health of children. One study conducted in Western Sydney (Jalaludin et al., 1996) found an association between reduction in lung function and PM_{10} levels in a sensitive group of children with asthma. Associations were also found with O_3 but with a different group of children. Maximum reduction in lung function was observed on high pollution days.

The second study was conducted in the Hunter and Illawarra regions (Lewis et al., 1996) and looked at the effects of TSP and SO_2 on respiratory symptoms in children. The aim of this study was to see if children living in high pollution areas had a higher incidence of cough, wheeze, chest colds etc., than those living in low pollution areas. A strong relationship was found between PM_{10} levels (derived from TSP measurements) and the incidence of cough at night (not associated with a cold). Increasing levels of PM_{10} between the lowest to the highest (an increase of 120%) was associated with a doubling in the frequency of cough at night. There was also a small, non significant effect on wheeze.

Estimates of the effects of particulate air pollution in Christchurch has suggested that PM_{10} may be responsible for up to 82,345 restricted activity days per year (Foster, 1996).

Summary of Associations Between Particulate Matter and Respiratory Symptoms and Lung Function

Studies of respiratory illness in children have shown associations with particulate matter at current ambient levels. The effects on pulmonary function as measured by FEV and FVC appear to be transient but may persist for periods of days to weeks after exposure. Respiratory symptoms such as cough, wheeze etc., have also been associated with exposure to particulates. The impact on the risk of developing respiratory illness as adults is still unclear. Long-term exposure to moderate to high levels of particulates has been shown to increase the risk of developing COPD in non-smoking adults. As with the mortality and hospital admissions studies, many studies are still finding no association.

Exposure to high levels of particulates has also been associated with absences from school and restricted activity days.

Toxicological Studies

Particle size is the most important characteristic influencing the deposition of particles in the respiratory system. Models of inhaled particle deposition relate aerodynamic diameter to the site of the deposition. Most inhaled particles of greater than 5 μm aerodynamic diameter deposit in the upper airways or larger lower airways. Particles smaller than 5 μm aerodynamic diameter are more likely to deposit in the smaller airways, eg., the bronchioles and the alveoli.

Particle clearance is achieved by several mechanisms. Particles deposited in the trachea and bronchioles rise on the mucocilliary ladder to be expelled by coughing or to be swallowed. Particles deposited beyond the terminal bronchioles are cleared largely by lung macrophages that, in turn, transport the ingested particles onto the mucocilliary ladder or into the lymphatic system (Harmsen et al, 1985). A small fraction of these distally deposited particles migrate through alveolar tissue directly into the lymphatic circulation. When ultrafine particles are inhaled, ie., those about 0.2 μm in diameter, highly increased interstitial access and acute inflammatory reaction have been demonstrated by lung lavage parameters (Oberdorster et al., 1992).

Biologic effects of a particle are determined by the physical and chemical nature of the particle itself (particularly its solubility), the physics of deposition and distribution in the respiratory tract, and the physiological events that occur in response to the particle's presence. Controlled human studies have focused on airway effects of single agents or simple mixtures. Toxicological studies have generally focused on single agents (eg., silica and asbestos) and on the effects on site of deposition or distribution (airways, alveoli). Most data have been collected on acid aerosols, ultrafine metal particles, asbestos, silica and diesel particles. These studies have been conducted mainly on animals but a considerable amount of data has been obtained from occupationally exposed workers. The exposures involved in these studies have been very high compared to ambient exposures and because of this caution must be applied in extrapolating the results to the general population.

Results of the animal studies have indicated that the site of respiratory tract deposition (and hence particle size) clearly influence the health outcome and that the toxicity is dependent on the chemical species. No human studies to date have shown any clear link between particle exposure and adverse health outcomes.

Human Exposure Studies:

Human clinical exposure studies utilise controlled laboratory conditions to test responses to atmospheric pollutants. Advantages include the opportunity to study the species of interest, humans, and the ability to control the atmosphere

with regard to pollutant concentration, aerosol characteristics, temperature and relative humidity. Concentrations can be varied while other conditions are held constant to determine exposure-response relationships. Mixtures of pollutants can be used to elucidate interactions.

Several factors limit the utility of human clinical studies. To meet legal and ethical requirements, exposures must be without significant harm. Studies are typically limited to short-term exposures, as long-term exposures are impractical and more likely to cause harm. Sample sizes are small and therefore may not be representative of populations at risk. Finally, the populations at greatest risk, (ie., the very young or elderly, people with existing respiratory or cardiovascular disease) have not been studied. Therefore the data from human clinical studies must be used in conjunction with data from animal studies and epidemiologic studies when aiming to conduct a health assessment.

Several health endpoints are used in human clinical controlled studies. Respiratory symptoms and pulmonary function tests are the most commonly used. These endpoints are also used in epidemiological studies and therefore allow a direct comparison between the two types of studies. Airway responsiveness is another commonly used endpoint. Airway responsiveness measures the change in lung function in response to bronchoconstricting agents such as methacholine or histamine. Asthmatics almost always have hyper-responsive airways. Other endpoints include measurement of mucocilliary clearance and sampling of the lower respiratory tract using fibreoptic bronchoscopy and bronchoalveolar lavage. Mucocilliary clearance is measured using radiolabelled aerosols.

The majority of human clinical studies have focused on pulmonary function effects of exposure to acid aerosols. Human exposure studies of the effects of acid aerosols were reviewed in the Acid Aerosols Issue Paper (US EPA, 1989) and the following conclusions were reached:

1. In healthy subjects, no effects on spirometry have been observed after exposure to concentrations of H_2SO_4 less than 500 $\mu g/m^3$, and no consistent effects have been observed at levels up to 1,000 $\mu g/m^3$ with exposure durations up to 4 hours. Studies of a variety of other sulphate and nitrate aerosols have similarly demonstrated an absence of spirometric effects on healthy subjects.
2. Combinations of sulphates with ozone or SO_2 have not demonstrated synergistic or interactive effects.
3. Asthmatic subjects experience modest bronchoconstriction after exposure to approximately 400 to 1000 $\mu g/m^3$ H_2SO_4 and small decrements in spirometry have been observed in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$ for 30 min.
4. Some studies suggest that delayed effects may occur in healthy and asthmatic subjects following exposure to H_2SO_4.

5. Effects of sulphate aerosols are related to their acidity, and neutralisation by oral ammonia tends to mitigate these effects.
6. Exposure to H_2SO_4 at concentrations as low as 100 $\mu g/m^3$ for 60 min alters mucocilliary clearance.
7. Airway reactivity increases in healthy and asthmatic subjects following exposure to 1,000 $\mu g/m^3$ H_2SO_4 for 16 min.
8. Differences in estimated respiratory intake explain only a portion of the differences in responses among studies.

There have been several studies since 1988 investigating the effects of acid aerosols on human respiratory health. The data in general support the findings in the Acid Aerosol Issue Paper with the majority finding no association between exposure to acid aerosols and adverse effects on lung function, respiratory symptoms, airway responsiveness or asthma. The studies that did show a correlation were conducted at very high levels of acid aerosol with no comparison to ambient conditions (US EPA, 1996).

The conclusions from these studies were that for healthy, young adults, brief exposures to H_2SO_4 at mass concentrations more than an order of magnitude above ambient levels (ie., up to 2,000 $\mu g/m^3$ for 1 hr) do not alter lung function, even with exercise and acidic gargles to minimise neutralisation by oral ammonia. Some subjects report increased lower respiratory symptoms, including cough, at 1000 $\mu g/m^3$ and higher levels, particularly with larger particle sizes (> 5 μm). The elderly and individuals with COPD do not demonstrate decrements in lung function at low levels of exposure ($\approx$ 82 $\mu g/m^3$). Acid aerosols alter mucocilliary clearance in healthy subjects, with effects dependent on exposure concentration and the region of the lung being studied. There are no data on the responses to particle exposure for healthy adolescents or children.

Asthmatics appear to be more sensitive to the effects of acid aerosols on lung function, but the effective concentrations differ widely. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to acid aerosols at exposure levels only slightly above peak ambient levels. Even in studies reporting an overall absence of effects on lung function, some asthmatic subjects appear to demonstrate clinically important effects. Two studies have suggested that responsiveness to acid aerosols may correlate with the degree of baseline airways hyperresposiveness. Two recent studies have examined the effects of acid aerosols and ozone on lung function in healthy and asthmatic subjects. Both studies found evidence that 100 $\mu g/m^3$ H_2SO_4 may potentiate the response to ozone. This finding is in contrast to results of previous studies (US EPA, 1996).

Studies conducted on human exposure to nitrate aerosols have shown that there is no effect on lung function at nitrate levels in ambient air on either healthy or asthmatic subjects. Studies conducted on subjects with influenza virus have shown that at high nitrate concentrations decreases in lung function are

observed. This study suggests that the presence of acute viral respiratory tract infection may render humans more susceptible to the acute effects of nitrate aerosols. Nevertheless, the concentration of nitrates used in this study were more than 100 times higher than ambient levels.

In general human studies other than acid aerosols provide insufficient evidence to draw conclusions regarding health effects. However, available data suggest that the inhalation of inert particles in the respirable range, including three studies of carbon black, have little or no effect on symptoms or lung function in healthy subjects at levels above peak ambient levels.

In recent years there have been several epidemiological studies linking exposure to airborne particles and lung cancer (Dockery et al, 1993; Pope et al ,1995). These studies show that after controlling for cigarette smoking and other major risk factors, there is evidence of an association between ambient air pollution and lung cancer. However, most investigators believe that the evidence to date does not support causality. One of the methodological problems with the epidemiological studies is that exposure of individual is not directly monitored. This is a difficult problem to solve, because of the complex nature of ambient particulate matter, the uncertainty concerning which components may be responsible for any carcinogenic effect, and the potential for confounding occupational or lifestyle factors, such as smoking and diet, that may affect an individuals exposure to carcinogens. One approach that has been undertaken is to use the adducts of DNA and PAHs as biomarkers to aid in the assessment of individual exposure to one class of potential carcinogens in airborne particulate matter. PAHs are thought to initiate cancer via covalent modification of DNA. This has led to a number of studies that have examined the presence of PAH-DNA adducts in white blood cells as a means of quantifying the biologically effective dose of PAHs in humans exposed to a variety of particulates (Hemmincki et al, 1990; Perera et al, 1992; Grzybowska et al, 1993). A study conducted in Poland investigated the PAH-DNA adducts in three groups: one occupationally exposed to particulates from coke ovens; residents of a town exposed to emissions from coke oven plants; and residents of a rural area not exposed to coke oven plant emissions (Hemmincki et al, 1990). Levels of PAH-DNA adducts were similar in both the plant workers and residents of the town, but 2-3 times lower in the residents of the rural area during the winter months. Blood samples taken during the summer showed that the levels of the town residents were lower than the coke oven workers and similar to the rural residents (Grzybowska et al., 1993). The use of coal for home heating during the winter months was thought to account for these seasonal differences.

PAHs have also been shown to affect the immune system (Albright and Goldstein, 1996). PAHs may function as potent immunosuppressive agents that can act directly on B and T lymphocytes. It has been shown that exposure to TCDD interrupts the normal production of thymocytes and the T cells that they generate in both fetal and adult thymus. This effect is provoked through a receptor, termed aromatic hydrocarbon receptor (AhR), located in the

cytoplasm of various types of cells. The AhR interacts with and selectively binds a range of PAHs. The binding affinity of the AhR is strongly influenced by a single gene. The mechanism that results in alterations of immune functions by PAHs nearly always involves transport of the AhR, together with a closely associated partner molecule (the AhR-nuclear translocator), to the nucleus of the cell, where it interacts with an element of a gene complex known as the xenobiotic responsive element. This initiates the production of certain enzymes which in turn alter the PAH molecule, rendering the molecule non-toxic or producing secondary substances that are toxic to cells, mutagenic or carcinogenic. Some of these substances may also alter genes or gene expression.

Nitro PAHs have been found in the lungs of one Japanese and six Chinese non smokers who died of lung cancer (Tokiwa et al., 1994). The Japanese patient had been exposed to combustion byproducts of heavy oil used for heating over a period of 10 years. Major mutagens found in the resected lung of this patient were 1-nitropyrene, 1-nitro-3-hydroxypyrene, 1,3-dinitropyrene and chrysene. The Chinese patients had been exposed soot or tar from coal combustion indoors. Four PAH were identified in resected lung tissue: benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene and pyrene. In this study 54 samples of lung tissue from other patients were analysed for background distribution of mutagen. No detectable PAH were present in these lung tissue samples.

Significant differences are observed in PAH-DNA adducts between individuals. It has been proposed that this may be due to different metabolic activities (eg., PAH metabolism or DNA repair) in addition to individual differences in exposure levels (Kriek et al., 1993; Lewtas et al, 1993). It has been proposed (Heussen et al, 1994) that exposure to low levels of PAHs may not increase the levels of PAH-DNA adducts significantly and may make detection difficult. Use of PAH-DNA adducts for use as a biomarker for general airborne particulate matter is further limited by the complexity of its make-up and potential variability across locations.

One source of particulate matter that has received considerable attention is diesel exhaust. Diesel exhaust is classified as a class 2A carcinogen, but has also been associated with other health problem particularly those associated with the respiratory tract (US EPA, 1996). Short-term exposure to high levels of diesel exhaust has been associated with mucous membrane, eye and respiratory tract irritation (including chest tightness and wheezing) and neuropsychological effects of headache, lightheadedness, nausea, heartburn, vomiting, weakness, and numbness and tingling in the extremities. Diesel exhaust odour can cause nausea, headache and loss of appetite. Most data regarding the effects of diesel exhaust have been obtained from occupationally exposed workers. Symptoms such as burning and watering of the eyes, laboured breathing, cough, chest tightness and wheezing, have been reported but no reductions in pulmonary function have been associated with exposure to diesel exhaust. Acute toxic effects caused by exposure to diesel exhaust are mainly attributable to the gaseous components (ie., mortality from carbon monoxide poisoning and lung

injury from respiratory irritants). When the exhaust is diluted to limit the concentrations of these gases, no acute effects are seen.

Chronic exposure to diesel exhaust has been associated with a higher prevalence of respiratory symptoms, primarily cough, phlegm or chronic bronchitis in occupationally exposed workers. Reductions in several pulmonary function parameters including FVC and FEV$_1$, have been reported.

Animal Studies

Animal studies have shown that acidic sulphates exert the greatest effect on the respiratory tract, with the response and location dependent upon particle size and mass and number concentration. At very high concentrations, much higher than ambient levels, mortality will occur following acute exposure, due primarily to laryngeal or bronchial constriction. Larger particles are more effective in this regard than smaller ones. Extensive pulmonary damage, including oedema, haemorrhage, shedding of the surface of the epithelium, and atelectasis (a collapsed or airless condition of the lung) can also cause mortality, but even in the most sensitive of animals, concentrations causing mortality are quite high.

A large number of animals studies have shown that both acute and chronic exposure to $H_2 SO_4$, at levels well below lethal doses, produce functional changes in the respiratory tract. Acute exposure alters pulmonary function largely due to bronchoconstrictive action, with the lowest effective level observed in guinea pigs of 100 $\mu g/m^3$ for a 1 hour exposure. Severe morphologic alterations in the respiratory tract have been reported to occur at high acid levels. Chronic exposure has also been associated with alterations in pulmonary function (eg., changes in the distribution of ventilation and in respiratory rates in monkeys). The main response to chronic exposure to low levels of H_2SO_4 is hypertrophy and/or hyperplasia of the mucus secretory cells in the epithelium. Hyper-responsive airways have been induced in rabbits after repeated exposure to 250 $\mu g/m^3$ H_2SO_4 .

Exposure to H_2SO_4 at levels less than 1,000 $\mu g/m^3$ has been shown to alter lung defence mechanisms. Defenses such as resistance to bacterial infection may be altered even by acute exposure to concentrations of H_2SO_4 around 1,000 $\mu g/m^3$. The bronchial mucocilliary clearance system is very sensitive to inhaled acids and fairly low levels of H_2SO_4 produce alterations in mucocilliary transport rates in healthy animals. The lowest level shown to have such an effect is 100 $\mu g/m^3$ with repeated exposures.

The assessment of the toxicology of acid aerosols requires some examination of potential interactions with other pollutants. Although such interactions may be antagonistic, synergistic or additive, the exact mechanism by which they occur

is not well defined. Low levels of H_2SO_4 (100 μg/m^3) have been shown to react synergistically with O_3 in simultaneous exposures using biochemical endpoints. In this case, H_2SO_4 enhanced lung damage due to O_3. Last et al., (1986) has proposed that the lowering of pH at the site of impaction of acid aerosols extends the life of free radicals generated by interaction of ozone with cells of the lung lining layer.

A recent study by Godleski et al., (1996) has shown that exposure of rats with chronic bronchitis to concentrated $PM_{2.5}$ from ambient air for 6 hrs on 2 consecutive days, leads to an increase in mortality. Similar results were not observed in healthy animals. The results of this study indicate that inflammation of the airways as well as airway constriction appear to be important in the response.

Studies of the potential of particles to cause cancer as well as nonmalignant respiratory effects have been studied in laboratory animals. All major types of airborne particulate matter may contain adsorbed organic compounds which may enhance the toxicity of the particles. Specifically these compounds may be mutagenic or carcinogenic to animals and may contribute to some extent to the incidence of cancer in humans associated with exposure to air pollution. Polycyclic aromatic hydrocarbons (PAH) are perhaps the best studied class of potential carcinogens in particulate matter. PAHs are mainly associated with the finer fraction (< 1μm) of particles. In addition to absorbed organic compounds, particles themselves have been found to induce a carcinogenic response. Inhalation of talc and carbon black aerosols have been associated with induction of lung tumours. Furthermore, it has been suggested that the carbon core of the diesel particle is at least as important as the organic compounds and possibly more so for lung tumour induction at high particle concentrations (> 2000 μg/m^3).

A total of 10 different long-term (> 1 year) animal inhalation studies of diesel emissions have been conducted (US EPA, 1995). The focus of these studies has been on the respiratory tract effects in the alveolar region. Effects in the upper respiratory tract and in other organs were not found consistently in chronic animal exposures. The respiratory system response has been well characterised in terms of histopathology, biochemistry, cytology, pulmonary function and respiratory tract clearance and the pathogenic sequence following the inhalation of diesel particles has been reported. The major mode of action appears to be alteration of the macrophage lung clearance mechanisms. There is a substantial body of evidence for an impairment of particulate clearance from the bronchio-alveolar region of rats following exposure to diesel exhaust. The result of the pathogenic processes may result in the presence of pulmonary inflammatory, fibrotic or emphysematous lesions. The non-cancer toxicity of diesel exhaust is considered to be due to particles and not the gas phase, since long-term effects seen with whole diesel are not found or are found to a much lesser extent in animals exposed to similar dilutions of diesel exhaust filtered to remove most of the particulate matter. Chronic studies in rodents have demonstrated

pulmonary effects at 200 to 700 $\mu g/m^3$ with a no effect level of 60 to 260 $\mu g/m^3$ being reported.

The possible toxicological role of ultrafine particles is of growing concern. It has been established that the greater part of the mass of metal ions formed in combustion processes is associated with ultrafine particles. Furthermore, the greater proportion of the condensed metal constituents are associated with the surface layers of these particles and would be readily available for chemical interactions with adsorbed materials and for rapid dissolution when deposited upon the liquid lining of the respiratory surfaces. Metals have been reported to affect clearance and other host defence systems. Nickel inhalation has been shown to impair macrophage function and increase the incidence of pneumonia in laboratory animals. Loading of particles with certain transition metals, such as iron, may have the potential to enhance particle toxicity, acute inflammation, and nonspecific bronchial responsiveness. Silica particles have been reported to be rendered more toxic when complexed with iron.

A large body of information has focused on the toxicology of other constituents of particulate matter such as metals, trace elements and silica. Metals contained in particulate matter are all toxic under specific conditions of exposure. Many are carcinogens as well as causing decreases in respiratory function. In addition, silica has been reported to cause lung tumours following chronic exposure in rats. The presence of high concentrations of metal ions and other adsorbed/condensed chemicals on the surface of particles deposited in the pulmonary region will clearly have a major influence on the toxicological response induced. Adsorbed gases may be catalytically converted to other products which may, or may not, be more toxic than the parent compound. The salts of manganese, vanadium and iron (II) have been shown (Amdur et al, 1968) to potentiate the response to SO_2, and at concentrations of 14-18 $\mu mole/m^3$ of metal, they increased the response by 3-4 fold. These metals are known to catalyse the oxidation of SO_2 to sulphuric acid.

Detailed reviews of the toxicology of particulate matter are given in the various US EPA Criteria Documents on Particulate Matter (US EPA 1996a-c; US EPA, 1996d), and in "Non-biological Particles and Health" (DoH, 1995).

Possible Mechanisms of Action for Health Effects Associated with Ambient Levels of Particulate Matter:

Substantial uncertainty still exists as to how particles, alone or in combination with other atmospheric pollutants, produce physiological and ultimately pathological effects. Because both the population affected and particulate matter are heterogenous, the mechanism(s) of action may also be diverse. Both fine and coarse fraction particles have the potential for deposition in the

tracheobronchial and alveolar regions of the respiratory system and thus have access to potential respiratory targets. Potential mechanisms of toxicity for particles has been summarised as follows (US EPA 1982):

- Chemical and mechanical irritation/stimulation resulting in bronchoconstriction by a variety of coarse and fine particles;
- Enhanced sensitivity to subsequent bronchoconstrictive agents by sulphuric acid;
- Altered clearance rates, increased mucous production by deposited material, including cigarette smoke, sulphuric acid, and dusts;
- Increased deposition and slowed clearance at bronchial bifurcations;
- Direct damage to tissues by acids;
- Decreased oxygen transport and probable increased resistance of blood flow through the pulmonary capillaries;
- Death of macrophages resulting in release of proteolytic enzymes that damage alveolar tissues, by silica and other coarse dusts;
- Damage to macrophages, other host defence mechanisms toxic materials coating the surface of the particles;
- Combined effect of exposure and slowed clearance of particles; and,
- Enhancement of damage to lung function by childhood respiratory infections.

To date none of these mechanisms have been proven and many of the studies supporting these suggestions involve exposures considerably higher than encountered under ambient conditions. More recently potential mechanisms for the toxicity of particles have been advanced and one major area of interest is in pulmonary inflammation. Mechanisms for induction of inflammatory response have been described for: (1) aerosol acidity (Lippmann 1989); (2) presence of ultrafine particles (Seaton et al, 1995); (3) transition metal ions (Tepper et al, 1994); and (4) active free radicals (Li et al, 1996). The most serious effects observed in epidemiological studies of the effects of particulate matter appear to be found in individuals with preexisting conditions. Given that immunological effects can be rapid, consistent with the period between increased exposure to particles and an acute effect such as mortality, it is plausible that inflammation can amplify and spread the response from small amounts of particulate matter. Several of the risk factors for toxicity of particles involve inflammatory responses (eg., asthma, COPD and infection). Several animal studies have shown that preexisting inflammation (eg., from ongoing infection) can amplify the inflammatory response to particles from a variety of sources (Costa et al, 1995; Lipfert, 1994).

Seaton et al (1995) have proposed the hypothesis that the mechanism of particles involves an inflammatory response by ultrafine particles (<0.02 μm diameter). As a result, mediators are released capable of causing exacerbation of lung disease in susceptible individuals and increased coagulability of the blood. This

mechanism provides a rationale for the increase in cardiovascular deaths observed during periods of high particulate air pollution. Low grade inflammation has been hypothesised to be particularly important in altering the coagulability of blood as a result of activation of mononuclear cells in the lung (MacNee and Selby, 1993). In support of Seaton's hypothesis is the observation that ultrafine particles cause greater inflammation (assayed by broncho-alveolar lavage) than larger particles of the same substance (Chen et al., 1992; Orberdorster et al., 1992). Fine particles have been shown to be taken up by epithelial cells (Stringer et al., 1995) and lung macrophages (Godleski et al., 1995) They have also been shown to produce inflammation in vitro (Dye et al, 1995) and in vivo (Kodvanti et al., 1995).

A further theory that has been postulated to explain the apparent link between cardiovascular deaths and airborne particulate matter involves solubilisation of fine particles which can diffuse in the parenchyma (Burnett et al, 1995). It is proposed that the chemical composition of the particle should affect not only the macrophages but also various cell populations, including endothelial and epithelial cells, and disseminate systematically via the bloodstream. These authors suggest that nanomolar amounts of some chemicals, eg., metals, may interfere with regulation metabolic activities of the lung endothelium, with an indirect effect on coronary circulation, or act directly on coronary vasculature. Clear experimental evidence for such effects remains lacking.

Aggravation of severity of underlying chronic lung disease has been hypothesised to explain increases in mortality (US EPA, 1996a-c; US EPA 1996d). Under such a scenario individuals experience more frequent and severe symptoms of their preexisting disease or a more rapid loss of function. Impaired respiratory function may be one way that particulate matter exerts effects. Several studies have indicated that aggravation of asthma symptoms is more strongly associated with fine particles than with larger ones (Thurston et al, 1994b; Ostro et al, 1991; Perry et al, 1983; Kleinman et al, 1995). Schwartz and Morris (1995) have suggested that the effects of particulates on cardiovascular disease may result from the result of airway obstruction and bronchial hyper-responsiveness which is associated with left ventricular function. They suggest that particulates may exacerbate the underlying obstruction and airway hyper-responsiveness may exacerbate this effect. Animal studies suggest that pulmonary hypertension may increase susceptibility to the effects of particulates on the lungs (Costa et al, 1994). These effects have the potential to diminish oxygenation of the blood and increase demand on the myocardium (Schwartz and Morris, 1995). This increased demand could precipitate myocardial ischaemia or infarction as well as heart failure.

Another hypothesis for the mechanism of particle effects involves accumulation of large lung burdens of poorly soluble particles. Large lung burdens of particles of even relatively low toxicity have been shown to cause lung cancer in

rats (Mauderly et al ,1994). Populations with prior exposure to large particle concentrations such as smokers, workers exposed to high particle levels, or those living in highly industrialised cities with a history of numerous increases in ambient particle concentrations have increased risk of mortality from exposure to particulates (US EPA, 1996a-c). Therefore, while current evidence does not support the mere accumulation of large burdens of particles in the lung as a mechanism for reported effects, it is plausible that increased particle burdens from past exposure could further augment the insult from recent increases in ambient particle concentration.

Impaired respiratory defence has also been proposed as a contributing factor to the toxicity of particulate matter. Patients with pneumonia have increased risk of mortality and morbidity from exposure to particulate matter. Cough, bronchitis and lower respiratory illness have also been associated with increased ambient particle levels. Both mucocilliary transport and macrophage function are critical to the host defence against inhaled pathogens. Increased risk of infection has been associated with changes in mucocilliary clearance (eg., excessive mucus secretion into the airways can cause airway blockage and reduced clearance). Alveolar macrophages are the primary defence cells of lungs and the impairment of their function would be expected to increase risk of infection. Clearance and macrophage function have been shown experimentally to be affected by constituents of particulate matter, notably fine aerosols (US EPA, 1996a-c; US EPA, 1996d). When bacteria are injected into lungs, particulate suspensions have been shown to increase bacterial infectivity, an effect that correlates with toxicity to alveolar macrophages in culture (Hatch et al, 1985). It has been suggested that while impaired host defence may not be plausible as a mechanism for mortality associated with short-term fluctuations of particle levels, it may contribute to long-term mortality.

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APPENDIX 6 -
HEALTH EFFECTS OF SULFUR DIOXIDE

SUMMARY[#]

Sulfur dioxide (SO_2) exposure results in the development of an acute irritant response initially in the upper airways (nose, throat, trachea and major bronchi) leading to coughing, wheezing, sputum production, increased incidence of respiratory infections, aggravation of asthma and chronic obstructive airways diseases, with resultant measurable increases in community patterns of respiratory and cardiovascular morbidity and mortality. The asthmatic population is at particular risk, and experimental studies have repeatedly demonstrated that SO_2 exposure in susceptible individuals can result in a rapid onset of symptoms and impairment of respiratory function within 10 - 15 minutes of exposure. Goals or guidelines need therefore to provide for adequate short-term protection for those susceptible individuals in the community, and it is suggested that an appropriate short-term goal or guideline should be in the vicinity of 0.175 ppm (500 $\mu g/m^3$). Longer-term goals or guidelines also need to be considered to protect both susceptible groups as well as the community as a whole in order to reduce overall the incidence of averse long-term effects of SO_2 exposure. It is therefore desirable to consider both daily (24 hour) and annual protective goals or guidelines, and it is suggested that appropriate values should be for a 24 hour protective goal or guideline 0.04 ppm (125 $\mu g/m^3$), and for an annual protective goal or guideline 0.02 ppm (50 $\mu g/m^3$).

Protective Ranges

Sulfur dioxide (SO_2) results, in the context of urban pollution, from the combustion of sulfur-containing fossil fuels such as coal and heavy oils. SO_2 has a direct irritant effect on the human airway, causing stimulation of protective nerve endings in the upper larger airways in the first instance. Individuals whose air passages are especially susceptible to irritant stimuli (asthmatics of all ages, those with chronic bronchitis and related conditions, and others who have compromised cardio-respiratory function) frequently respond by developing increasing coughing, chest tightness, wheezing, and aggravated sputum production. There is are considerable differences in the concentrations of SO_2 required to produce acute irritant responses in those individuals who have normal patterns of airway reactivity (1.0+ ppm), and in those individuals who have significantly increased airway reactivity such as asthmatics (0.2 -0.3 ppm).

At a community level, these individual irritant responses to SO_2 are manifest as an increasing frequency and severity of asthma, increased hospital admissions, aggravation of underlying respiratory infections, resulting in increases in both morbidity (illness) and mortality (death). In many instances, it is difficult, and at

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[#] Prepared by Dr. Jonathan A. Streeton, FRACP.

times impossible, to separate the adverse effects resulting from SO_2 exposure from those effects resulting from concurrent exposure to mixtures of other known irritant pollutants such as respirable particles, nitrogen oxides, and ozone. Prior exposure to other pollutants is now recognised as resulting in a general accentuation of airway responses to other irritant stimuli, including allergens such as grass pollens, house dust, animal danders and the like. A useful review of the current understanding of the effects of mixtures of pollutants can be found in DoH 1995b *("Health Effects of Exposures to Mixtures of Pollutants").*

SO_2 acts directly on the larger upper airways (nose, throat, trachea, and major bronchi) in the first instance, responses tend to be generally rapid in onset, occurring within a few minutes, and achieving maximum effect within 10 - 15 minutes, particularly in those individuals with significant increases in airway (bronchial) reactivity, such as asthmatics and those suffering from other similar bronchospastic conditions.

These responses can be manifest either symptomatically as wheezing, chest tightness, shortness of breath or coughing; or functionally as reductions in ventilatory capacity ($FEV_{1.0}$, increased specific airway resistance[sRAW], or other like parameters of ventilatory function). If exposure to SO_2 should occur under exercise conditions, then the observed responses may well be accentuated due to increased ventilation associated with exercise, and the fact that soluble gases such as SO_2 will tend to carried much further down the respiratory tract before coming into contact with the lining mucus layer of the airways, the bronchial mucosa, resulting in the production of an irritant acidic solution which stimulates the sensory nerve endings (vagal afferents) leading to coughing and subsequently wheezing as a result of smooth muscle spasm.

There is a wide range of sensitivity present, both in normal individuals, and in those with asthma who recognised as being the most sensitive reactors to irritants such as SO_2. Whilst a threshold level has not yet been clearly defined, it is possible to demonstrate a pattern of continuous dose-response relationships. When considering protective ranges as part of guidelines or standards, it is clearly necessary to consider the minimum concentrations which can be identified with adverse effects, and for this purpose, it is usual to measure the responses occurring in asthmatics who are exercising in exposure chambers. It should be noted that the severity of the individuals asthma does not appear to greatly alter the pattern of response. In some studies, small changes were seen in airway resistance in a few asthmatic subjects at only 0.1 ppm ($286 \mu g/m^3$), however it is more usual to see minimal sub-clinical responses occurring at 0.2 ppm ($572 \mu g/m^3$), a 10% reduction in $FEV_{1.0}$ below baseline at about 0.4 ppm ($1144 \mu g/m^3$), and reductions of about 15% in $FEV_{1.0}$ below baseline occurring at about 0.6 ppm ($1716 \mu g/m^3$). These results apply to short term exposures in an exposure chamber of approximately 15 minutes duration, both at rest and whilst under exercise conditions.

There do not appear to be any significant differences in observed responses to exposures of longer durations up to about 24 hours. Longer term (or chronic) exposures are more generally reflected in community patterns of respiratory illness, the prevalence of respiratory symptoms, or differences in lung function between areas of high or low levels of SO_2, usually with differing levels of particulates. Most of these studies were undertaken in coal-burning areas, and resulted in the LOAEL for SO_2, in combination with particulates, being considered to be 0.035 ppm (100 $\mu g/m^3$) annual average exposure. With changes in fuel burning patterns, and in urban mixtures, more recent studies usually related to specific industrial sources of SO_2 and changing urban situations would suggest LOAEL even less than 0.035 ppm. In the past, the influence of fine particles on morbidity and mortality patterns was not recognised as it is now, and indeed it would seem likely that the major effects are more probably related to the particle load than to other pollutants such as SO_2.

Medium term exposures of the order of 24 hour's duration have been assessed mainly using epidemiological studies in which the effects of SO_2, particulates, and other associated pollutants are considered. These studies mainly focus on the production of symptoms in groups of selected sensitive subjects, with symptoms generally developing when SO_2 levels exceeded 0.087 ppm (250 $\mu g/m3$), usually in the presence of particulates (PM10). More recent studies however take more regard of changing social activity patterns and changes in SO_2 sources such as mixed industrial and vehicular sources. These further studies are now showing increasing effects on mortality (all causes, respiratory, cardiovascular), and on morbidity (emergency hospital admissions for respiratory illnesses, especially COPD) at considerably lower levels of exposure than were previously thought to be the case, such as daily levels usually exceeding 0.043 ppm (125 $\mu g/m3$), or mean annual levels not exceeding 0.017 ppm (50 $\mu g/m3$). In some studies, these patterns of response have been shown to persist even when particulates expressed even crudely as black smoke or as TSP have been allowed for. It should be also noted that no obvious threshold levels have as yet been identified in these later studies.

To summarise the results of the available exposure data:

- Short-term protective exposure guidelines over brief periods of 10 - 15 minutes need to be considered as there is clear evidence in controlled studies that exercising asthmatics can be expected to experience some changes in lung (pulmonary) function in association with respiratory symptoms after short periods of exposure. As SO_2 can frequently present as brief sharp peaks, depending on the characteristics of the local sources, it is not practicable to extrapolate these short exposure periods into longer averaging periods such as 1 hour. Currently, the body of opinion favours the suggestion that any short term guideline should not exceed a concentration of 0.175 ppm (500 $\mu g/m3$) averaged over 10 minutes.

- Daily and longer-term exposures leading to changes in morbidity, mortality, or to alterations in lung function need to be assessed on the basis of available epidemiological studies where individuals are exposed to mixtures of pollutants, which usually, but not necessarily, include particulates. Previously, it was usual practice to base health related guidelines or standards on the observed LOAEL, corrected by a safety (uncertainty) factor of two to ensure adequate protection of susceptible individuals. However, as already indicated, more recent studies suggest the possibility of significant adverse public health effects at levels considerably lower than had been previously envisaged (for example, a 24-hour guideline of 0.04 ppm/ 125 μg/m^3; or an annual guideline of 0.02 ppm/ 50 μg/m^3). There remains considerable uncertainty as to whether or not SO_2 is in fact responsible for the observed adverse health effects, or whether it might be acting as a surrogate for an as yet unidentified pollutant, possibly ultra-fine particles. There as yet insufficient data available on which to base any further tightening of guidelines from those detailed above, as these previously suggested guidelines should provide adequate protection for the 'at-risk' asthmatic population in Australia.

Editorial Comment [#]

Experimental studies have shown that individuals with asthma may develop symptoms and demonstrate decrements in lung function when exposed, during exercise, to SO_2 concentrations in the range 0.25 to 0.5 ppm (reviewed in Sandstrom 1995). No similar effects are seen in healthy, non-asthmatic individuals at SO_2 concentrations of up to 1.0 ppm (Schachter et al 1984).Marked variability exists among asthmatics in their individual sensitivity to sulfur dioxide (Horstman et al 1986). Responses to SO_2 are enhanced by prior exposure to ozone (Koenig et al 1990). The intensity of symptoms induced by performing moderate exercise during exposure to SO_2 at concentrations in excess of 0.5 ppm may be greater than those experienced by asthmatics during bronchospastic episodes triggered by more strenuous exercise in clean air (Gong et al 1995). Symptoms and bronchoconstriction may occur after exposure to SO_2 concentrations of 1.0 ppm during exercise for as little as two minutes (Horstman et al 1988). There is evidence that a substantial minority of asthmatics may experience bronchoconstriction after brief exposures, during moderate exercise, to SO_2 concentrations in the range 0.6 to 1.0 ppm (US EPA 1994a, 1994b). However, the effect reverses quickly with rest, even if exposure to SO_2 continues (Hackney et al 1984).

Epidemiological data on the human health effects of sulfur dioxide exposure is difficult to interpret because of the relationship between this exposure and particulate pollution. Whilst there are some localities where moderate to high levels of particulate pollution are seen with low levels of SO2, the reverse does not appear to be the case. Regional and temporal variations in SO2 levels are strongly correlated with variations in concentrations of respirable particles (for example, Sunyer et al 1996 calculated a correlation coefficient of 0.63 between SO2 and particles measured as Black Smoke for Barcelona). For this reason, unadjusted estimates of the effects of SO2 on health outcomes may be misleading. On the other hand, the degree of co-linearity makes the partitioning of effects between SO2 and respirable particles using methods involving regression analysis hazardous and unstable (Schwartz et al 1996).

Table 1 of this Appendix includes data from several European participants in the APHEA project (Katsouyanni et al 1995; APHEA 1996) who have recently reported on the relationships between daily variations in average SO2 levels (along with those of other pollutants) and various health outcomes. These studies supplement a number of earlier studies in Europe and the USA. Although the interpretation of individual risk from these collective studies is severely limited because only grouped exposure data are available, and there is considerable inconsistency in the findings (Concawe 1996), SO2 levels appear to be more important than particle concentrations in this context. Confounding by other variables such weather and other pollutants is also possible, so that for the majority of the studies, no consistent endpoint in terms of respiratory or cardiac morbidity or mortality can be deduced at this time.

Ambient SO2 levels are high in eastern and central Europe and China. In Poland, a substantial and significant independent relation between fluctuations in SO2 levels and daily cardiovascular and respiratory mortality has been demonstrated. In the Czech Republic, the effect on neonatal respiratory mortality, although large, is only of borderline statistical significance. High levels of SO2 were associated with increases in upper respiratory tract symptoms in former East Germany, and with impaired lung function in China, although this latter association was not adjusted for associated particulate pollution.

Significant associations between SO2 levels and daily mortality rates have also been shown in Philadelphia, Detroit, Athens, Lyon, and Barcelona where ambient levels are lower than in eastern Europe. However, of these case studies, only the data from Athens were adjusted for variations in levels of respirable particles (measured as black smoke) and remained significant after that adjustment.

There are data on the effects of SO2 exposure on hospital admissions and emergency room attendances for asthma and respiratory diseases. In Birmingham, UK there were significant independent effects of the weekly average SO2 levels on asthma admissions to hospital during winter and all respiratory admissions in autumn (Walters et al 1994, 1995). Other studies, in Helsinki (Ponka and Virtanen 1996) and in Barcelona (Sunyer et al 1996) did not adjust for other pollutants, but notwithstanding have drawn conclusions consistent with those reached in Birmingham.

There is no consistent evidence that long term levels of SO2 exposure influence the prevalence of symptoms or significantly affect lung function. The Havard Six Cities study (Dockery et al 1989) has shown that symptoms related to cough were more prevalent in the cities with higher SO2 levels, but these cities also had higher levels of other pollutants. The observed relationships between long-term SO_2 levels and COPD symptoms in California (Euler et al 1987) must be interpreted with similar caution. A large cross-sectional survey conducted in conjunction with NHANES II in the USA did not demonstrate any evidence of a cross-sectional relationship between SO_2 and lung function (Schwartz 1989).

In conclusion, the experimental evidence demonstrates that brief exposures to SO_2 concentrations of the order of 0.5 ppm may cause transient bronchoconstriction and symptoms in some asthmatics who exercise during the exposures. The epidemiological evidence shows that over a wide range of exposure levels, respirable particles and/or sulfur dioxide are associated with a range of adverse health effects including increases in both daily mortality and hospital admission rates. At this point in time however, these adverse effects cannot confidently be attributed solely to either one or the other of these

pollutants, but rather these effects may result from interactions of mixtures of pollutants including SO2, respirable particles, NO2, and ozone (DoH 1995a, 1995b).

TABLE 1
Epidemiological Studies

Health Endpoint	Study Population	Lowest Level and Averaging Time	Upper Level and Averaging Time
MORTALITY	General	0.77 ppb mean 24 hour	328 ppb mean 24 hour
	Elderly	0.77 ppb mean 24 hour	56 ppb mean 24 hour
	Individuals with respiratory disease	0.77 ppb mean 24 hour	223 ppb mean 24 hour
	Individuals with cardiovascular disease	0.77 ppb mean 24 hour	223 ppb mean 24 hour
	Infants (postneonatal)	11.2 ppb	
HOSPITAL ADMISSIONS	Asthma	4.6 ppb mean 24 hour	44.2 ppb mean 24 hour 700 ppb long term
	Individuals with respiratory disease	7.7 ppb mean 24 hour	44.2 ppb mean 24 hour
	Individuals with COPD	13.7 ppb mean 24 hour 4.9 ppb max 1 hour	109 ppb mean 24 hour 252 ppb max 1 hour
RESPIRATORY SYMPTOMS AND LUNG FUNCTION:	Healthy Children	1.29 ppb annual average 0 ppb mean 24 hour 15.2 ppb max 24 hour	26 ppb annual average 106.8 ppb mean 24 hour 487.5 ppb max 24 hour
	Healthy Subjects	40 ppb 500 hours/yr	

LITERATURE REVIEW [#]

The health effects of SO_2 have been recognised for decades. High SO_2 and particle concentrations have been associated with increased mortality and morbidity in many major air pollution episodes such as those experienced in London in November 1952; in the Meuse Valley, Belgium during the 1930s; and at Donora, Pennsylvania in 1948. Early analyses of these episodes were unable to separate the effects of individual pollutants. With advances in statistical techniques, recent epidemiological studies have focussed on identifying health impacts due to specific pollutants. These studies have revealed increased mortality from respiratory and cardiovascular causes associated with ambient SO_2 levels found in various parts of the world. In addition associations between hospital admissions for asthma, COPD and respiratory disease have also been observed.

Controlled exposure studies have been extensively reviewed (Bascom et al 1996; DoH 1992; US EPA 1982, 1986a, 1986b, 1994a, 1994b; WHO 1987, 1995). Recent SO_2 exposure studies have shown that exercising asthmatics are sensitive to brief exposures to SO_2. Some respond with bronchospasm to as little as 0.25 ppm SO_2, whereas persons with normal patterns of bronchial reactivity may require exposure to concentrations of the order of at least 5 - 6 ppm SO_2 before they develop symptoms such as chest tightness, cough, or wheezing. Such exposures do not appear to cause delayed or prolonged effects.

This review summarises the data from recent epidemiological studies on the health impacts of SO_2. It should be noted that due to the correlation between particles and SO_2 in many of these studies, it is often difficult to isolate the effects of one pollutant from another, and that a large amount of this information has arisen from studies investigating the effects of particles on health. In addition, fine particulate SO_4^{2-} which arise from the conversion of SO_2 in the atmosphere have also been considered in this review.

Mortality

A study by Schwartz and Marcus (1990) revealed a highly significant relationship between daily mortality and SO_2 levels in London for the period 1958 to 1972. An association was also found for Black Smoke which was stronger than that observed for SO_2. When both pollutants were considered in the same model, only Black Smoke remained significant. A further study from London has shown that daily average SO_2 exposures were associated with daily mortality from all causes for the period 1987 to 1992 (Anderson et al 1996).

[#] Prepared by Dr. Lyn Denison, Ph.D., and reviewed/edited by Dr. Jonathan A. Streeton.

The average SO_2 level during the study period was 32 µg/m^3 with a maximum value of 100 µg/m^3. Significant associations were found during the warm season for 'all causes' mortality and all year for respiratory causes. These observations were found with a 1 day lag period. Stronger associations were observed for ozone and for Black Smoke.

Several studies have examined the association between air pollution and daily mortality in Philadelphia. A significant positive association was found between daily mortality (all causes) and SO_2 levels in Philadelphia for the period 1973 to 1980 (Schwartz and Dockery, 1992). The strongest associations were found with the mean SO_2 level of the current and the previous day. Total mortality was increased by 5% per 100 µg/m^3 increase in SO_2. An association was also found between TSP levels and daily mortality. When both pollutants were considered in the same model only TSP was significant. The mean daily average level of SO_2 during the study period was 21.0 ppb with a 95th percentile of 46 ppb.

Moolgavkar et al (1995a) examined the association between daily mortality and daily SO_2 and TSP levels in Philadelphia for the period 1973 to 1988. The results of their study, in contrast to those of Schwartz and Dockery, found associations between SO_2 and daily mortality for the spring, fall and winter which remained even when TSP was included in the model. The relative risks per 100 µg/m^3 increase in SO_2 were 1.19, 1.14 and 1.21 for spring, fall and winter respectively. The mean SO_2 levels during the study period ranged from 15.7 to 25.4 ppb, with maximum levels ranging between 100 and 156 ppb. The effect of TSP was greatly attenuated when SO_2 was added to the model.

In a study by Moolgavkar et al (1995b), both TSP and SO_2 were found to be associated with daily mortality in Steubenville, Ohio. Statistically significant associations were found even when both pollutants were considered simultaneously in the model although the observed effect of TSP was greatly attenuated. The mean SO_2 level during the study period was 28.8 ppb with a 90th percentile value of 58 ppb. The relative risk per 100 ppb increase in the mean SO_2 level of the previous day was 1.072. The strongest associations were observed during the winter. The results of this study are in contrast to those of an earlier study by Schwartz and Dockery (1992) which had found that when SO_2 was considered alone, significant associations with daily mortality were observed. However, when both pollutants were considered in the same model, the association with SO_2 became insignificant.

Schwartz (1991) found that in independent analysis both TSP and SO_2 were significantly associated with daily mortality in Detroit, but when both pollutants were considered, only TSP remained significant. The mean SO_2 level during the study period was 12 ppb with a 95th percentile value of 26.3 ppb. The strongest association was found for the previous day SO_2 level, with both the current day and preceding two days mean being insignificant.

A study by Katsouyanni et al (1990) has shown associations between daily mortality and air pollution (SO_2 and TSP) in Athens. Mean daily average SO_2 levels during the study period (1975 to 1982) ranged from 62.4 to 126.5 $\mu g/m^3$ with maximum values from 392 to 936 $\mu g/m^3$. The strongest association was found for mortality from respiratory causes.

In a subsequent study (Touloumi et al 1996), SO_2 levels in Athens during the period 1987 to 1991 were found to be associated with mortality from all causes. For a 100 $\mu g/m^3$ increase in daily average SO_2 levels, there was a 5% increase in mortality. The association was strongest during the winter when SO_2 levels were highest and when levels of Black Smoke were greater than 100 $\mu g/m^3$. The mean daily average SO_2 level during the study period was 51.3 $\mu g/m^3$ with a maximum value of 361 $\mu g/m^3$. Associations were also observed with both CO and Black Smoke. The results of this study confirmed the findings of an earlier study of the association between air pollution and daily mortality in Athens for the period 1984 to 1988 (Touloumi et al 1994). Daily average SO_2 levels were significantly associated with daily 'all causes' mortality. The mean daily average SO_2 level for the period 1984 to 1988 was 44.9 $\mu g/m^3$. The strongest association was observed for a 1 day lag period. Dose response curves showed a curvilinear response with a steeper slope at lower SO_2 levels. A decrease in SO_2 levels by 10% was estimated to decrease daily mortality by 0.65%.

In a study of daily mortality in Lyon, daily average SO_2 levels were found to be associated with mortality from respiratory and cardiovascular conditions (Zmirou et al 1996). The relative risks per 50 $\mu g/m^3$ increase in daily average SO_2 levels were 1.22 and 1.54 for mortality from respiratory and cardiovascular causes respectively. Associations were also found for PM_{13} but these were weaker than those observed for SO_2. The mean daily average SO_2 level during the study period (1985 to 1990) was 46.8 $\mu g/m^3$ with a maximum value of 635.7 $\mu g/m^3$. The strongest association was observed for a 1 day lag period but lags up to 3 days were still significant.

Daily average SO_2 levels have been associated with total, elderly, cardiovascular and respiratory mortality in Barcelona for the period 1985 to 1991 (Sunyer et al 1996). The relative risks per 100 $\mu g/m^3$ increase in daily average SO_2 level were 1.13 for total, elderly and respiratory mortality respectively, and 1.14 for cardiovascular mortality. The association between SO_2 and respiratory mortality was stronger during the summer than during the winter (relative risk 1.24 c/f 1.08). These associations were found with current day and one day lag periods. The mean 24 hour average SO_2 level during the study period was 41.2 $\mu g/m^3$ with values ranging from 2.2 to 160 $\mu g/m^3$. An association was also found between mortality and daily Black Smoke levels, however the associations with SO_2 were stronger than those with Black Smoke particularly for respiratory causes.

Significant associations were found between daily mortality from respiratory disease and circulatory disease in Cracow, Poland for the period 1977 to 1989

(Kryzanowski and Wojtyniak 1991/92). An increase in SO_2 levels of 100 $\mu g/m^3$ was associated with a 19% increase in deaths due to respiratory causes and a 10% increase in deaths due to circulatory causes. These effects were more pronounced in the elderly.

Associations between daily SO_2 levels and neonatal and postneonatal mortality were found in a study from the Czech Republic for the period 1986 to 1988 (Bobak and Leon 1992). The strongest effects were observed for postneonatal respiratory mortality. The mean SO_2 level during the study period was 31.9 $\mu g/m^3$. An association was also observed for TSP.

A study from Sao Paulo, Brazil found significant associations between daily SO_2 levels and mortality in the elderly (Saldiva et al., 1995). Associations were also found for PM_{10}, NO_x, and CO. However when all pollutants were included in the same model, only the association with PM_{10} remained significant. The mean daily average SO_2 level during the study period was 6.5 ppb.

In a prospective study of 552,138 US adults, Pope et al (1995) found strong associations between mortality from cardiopulmonary causes and lung cancer with fine particles and particulate sulphates. Mortality from lung cancer was found to be more strongly associated with sulphates than with a general fine particle measure. The risk ratios for all causes, for lung cancer alone, and for cardiopulmonary deaths per 19.9 $\mu g/m^3$ increase in sulphates were 1.15, 1.36 and 1.26 respectively. The corresponding risk ratios for $PM_{2.5}$ were 1.17, 1.03 and 1.31 respectively. These associations persisted even after controlling for age, sex, race, cigarette smoking, exposure to passive cigarette smoke, body mass index, drinks per day of alcohol and occupational exposure.

Hospital Admissions and Emergency Room Visits

Daily and weekly SO_2 levels have been associated with hospital admissions for asthma and respiratory disease in Birmingham, UK (Walters et al 1994). During the winter months this association was observed with a 2 day lag period, but during the summer and autumn no lag was observed. The results of this study suggest that a 100 $\mu g/m^3$ increase in daily SO_2 levels may give rise to 4 more asthma admissions and 15.5 more respiratory admissions each day. The mean daily SO_2 level was 39.1 $\mu g/m^3$ with a maximum level of 126.3 $\mu g/m^3$. An association was also found between Black Smoke and hospital admissions for both asthma and respiratory admissions during the winter.

A further study from the UK examined the relationship between attendance at hospital emergency departments for acute wheeze in children and daily SO_2 levels (Buchdahl et al 1996). A significant association was found between daily average SO_2 levels and emergency room visits with an increase of 12% per 14 $\mu g/m^3$ increase in daily average SO_2 level. The daily average SO_2 level during

the study period was 22 $\mu g/m^3$. Significant associations were also observed for ozone. A study from the West Midlands in the UK however found no association between hospital admissions for asthma and daily SO_2 or Black Smoke (Walters et al 1995), but did find significant associations however for NO_2.

An association between SO_2 levels and emergency room visits for COPD have been found in Barcelona for the period 1985-1986 (Sunyer et al 1993). An increase of 25 $\mu g/m^3$ in 24 hour average SO_2 levels was associated with a 6% and 9% increase in emergency room admissions for COPD in the winter and summer respectively. The strongest association was observed for the same day, and was weaker for a 1 day lag. The association had disappeared with 2-day lagged values. Similar associations were found for Black Smoke during the winter months but not during the summer. The mean 24 hour average SO_2 level during the study period was 49 $\mu g/m^3$ during the winter and 29 $\mu g/m^3$ during the summer. Similar results were found in an earlier study in Barcelona (Sunyer et al 1991). Daily emergency room visits for COPD increased by 0.02 per 1 $\mu g/m^3$ increase in daily SO_2 levels. The 24 hour average SO_2 levels during the study period ranged from 39 to 310 $\mu g/m^3$ with a yearly mean of 56.5 $\mu g/m^3$. One hour maximum values ranged from 14 to 720 $\mu g/m^3$ with a mean value of 141.9 $\mu g/m^3$. Statistically significant associations were also found for Black Smoke and CO.

In a further study from Barcelona, no association was found between SO_2 levels and emergency room visits for asthma (Castellsague et al 1995). Strong associations were found for both Black Smoke and TSP. Similar results were found in a study from The Netherlands in which no association was found between daily SO_2 levels and emergency room visits for respiratory disease (Schouten et al 1996). The mean daily average SO_2 level during the study period was 38 $\mu g/m^3$ with a maximum value of 381 $\mu g/m^3$.

A study from Helsinki found positive associations between hospital admissions for asthma and daily SO_2 levels in the 15 to 64 year, and the above 64 years age groups (Pönka and Virtanen 1996). The daily mean SO_2 concentrations ranged from 13 to 26 $\mu g/m^3$. The strongest associations were found for a 2 day lag period. In an earlier study in Helsinki, all admissions for asthma (including emergency room admissions) were significantly correlated with daily average SO_2 levels (Pönka 1991). Associations were also found for O_3, NO_2, NO, CO, and TSP. Among the elderly, SO_2 levels were correlated with admissions to emergency wards for asthma. The most significant association with SO_2 was found when the long-term SO_2 concentration exceeded 200 $\mu g/m^3$ (0.07 ppm). The mean concentration of SO_2 during the 3 year study period was 19.2 $\mu g/m^3$.

A weak association has been found between hospital admissions for respiratory illness and SO_2 levels in Cleveland, Ohio (Schwartz et al 1996). The relative risk per 100 $\mu g/m^3$ increase in SO_2 was 1.03. Associations were also found for ozone and for PM_{10}. The mean SO_2 level during the study period was 35 ppb.

Ambient particulate SO_4^{2-} have been associated with hospital admissions for cardiac and respiratory diseases in Ontario, Canada (Burnett et al 1995). A 13 $\mu g/m^3$ increase in SO_4^{2-} on the day prior to admission was associated with a 3.7% increase in respiratory admissions, and a 2.8% increase in cardiac admissions. Increases were observed for all age groups and were not affected after controlling for temperature and season. Sulphate levels ranged from 2 $\mu g/m^3$ to 7.7 $\mu g/m^3$ across the study region, with 99 th percentile levels ranging from 9 $\mu g/m^3$ to 33 $\mu g/m^3$. Sulphate levels were higher during the summer months.

Respiratory Symptoms and Lung Function

The development of symptoms and increasing severity of obstructive airways disease, chronic bronchitis and asthma were not associated with SO_2 levels but were associated with particulate SO_4^{2-} and other measures of fine particles in a cohort of non-smoking Seventh day Adventists (Abbey et al 1995a). Sulphates were statistically significantly associated with development of asthma and were more strongly associated with increasing severity in airways disease symptoms than were any of the other pollutants. The relative risks per 7 $\mu g/m^3$ increase in annual average SO_4^{2-} levels were 1.43 and 2.85 for obstructive airways disease and asthma respectively. The results of this study confirm the findings of an earlier study by Abbey et al (1993) where no association was observed between SO_2 levels and respiratory symptoms.

Sulphate particles have also been found to be associated with shortness of breath in asthmatics in Denver, Colorado during the winter of 1987 -1988 (Ostro et al 1991). Asthmatics were asked to keep a daily diary reporting symptoms of asthma status including moderate or severe cough, shortness of breath, medication use and other related information. The daily mean SO_4^{2-} level during the study period was 2.11 $\mu g/m^3$ with a maximum value of 12.7 $\mu g/m^3$. The mean SO_2 level was 14.1 $\mu g/m^3$ with a maximum value of 59.8 $\mu g/m^3$. No association was found for any outcome and SO_2.

As part of the Havard Six Cities study, the effects of ambient sulfur oxides and airborne particles on the respiratory health of children was examined (Ware et al 1986). Daily average TSP, particulate SO_4^{2-} and SO_2 levels were all associated with increased frequency of cough, and TSP and particulate SO_4^{2-} with bronchitis and lower respiratory illness in all study areas. The observed effects were greater in the more polluted cities. Yearly average SO_2 and particulate SO_4^{2-} levels ranged from 3.4 to 68.3 $\mu g/m^3$ and 5.4 to 18.8 $\mu g/m^3$ respectively, comparing the least and most polluted cities.

In a study from Steubenville, Ohio (Dockery et al 1982), increases in daily average SO_2 levels were found to be associated with decreases in pulmonary function in children. Levels of SO_2 ranged from 0 to 281 μg/m³ during the study period. The associated changes in FVC and $FEV_{0.75}$ over this range of SO_2 concentrations were -16 ml for FVC and -13 ml for $FEV_{0.75}$ respectively.

The risk of developing chronic obstructive airways symptoms (COPD) due to long-term exposure to ambient levels of SO_2 and TSP has been examined in a group of Seventh Day Adventists in California (Euler et al 1987). A statistically significant association between chronic airways symptoms and SO_2 were found for exposures above 4 pphm. An 18% increase in the risk of developing symptoms was observed for exposure at these levels for 500 hours/year. An association was also observed for exposure to TSP.

In a study by Queirós et al (1990), exposure to low but persistent levels of SO_2 for a period of months was found to lower the threshold of asthmatic children to other bronchospastic stimuli in Oporto, Portugal. In contrast, there was no correlation between daily levels of SO_2 (or Black Smoke) and asthmatic attack rates suggesting that at these levels neither of these pollutants directly induce bronchospasm. The mean SO_2 level during the study period (1983-1987) was 23.9 μg/m³ with a maximum daily mean of 83.5 μg/m³.

A study conducted in New South Wales to investigate the effects of emissions from power stations on asthma found no correlation between SO_2 levels and the prevalence of asthma in children (Henry et al 1991). SO_2 levels in the vicinity of the power station (Lake Munmorah) were considerably higher than those in the control area (Nelson Bay) with yearly average levels of 2 and 0.3 μg/m³ at Lake Munmorah and Nelson Bay respectively. Maximum daily averages were 26 μg/m³ and 11 μg/m³ at Lake Munmorah and Nelson Bay respectively, with maximum hourly averages of 139 μg/m³ and 43 μg/m³.

Another somewhat negative study from New South Wales just recently completed by Lewis et al (1996) assessed the respiratory health of children aged 8 to 10 living in the Hunter and Illawarra regions in relation to local air pollution. A multivariate analysis showed no significant effects for SO_2, but did show a significant effect of PM_{10} on chest colds (OR 1.019 [1.006 - 1.037]), and on night time coughing (OR 1.018 [1.011 - 1.025]). SO_2 levels ranged between 0.16 - 0.90 pphm (mean annual average), and PM_{10} ranged between 18.6 - 58.3 μg/m3 (annual average). The results also indicated that both maternal smoking and a history of maternal allergy had significant effect on the responses.

No association was found between daily SO_2 levels and respiratory symptoms in preschool children in Switzerland (Braun-Fahrlander et al 1992). Annual average SO_2 levels in the study region ranged from 8 to 70 μg/m³.

Both SO_2 and SO_4^{2-} were found to be associated with respiratory illness in children as part of the Havard Six Cities study (Dockery et al 1989). Reported rates of chronic cough, bronchitis, and chest illness were positively associated with both pollutants, however the association with SO_4^{2-} was stronger than that with SO_2. No association was found for either pollutant and asthma, persistent wheeze, hay fever or non-respiratory illness. In addition, no associations were found between either SO_2 or SO_4^{2-}, and any of the pulmonary function measures considered, namely: FVC, FEV, $FEV_{0.75}$ and MMEF. Yearly average SO_2 levels in the Havard Six Cities ranged from 3.5 to 27.8 ppb with SO_4^{2-} levels ranging from 3.2 to 13.9 $\mu g/m^3$. Associations were also found for TSP, PM_{15}, and $PM_{2.5}$.

In a study from East Germany, daily average SO_2 levels during the winter months were found to be associated with upper respiratory symptoms in children (Von Mutius et al 1995). The odds ratio associated with the mean SO_2 level for the development of upper respiratory symptoms was 1.72. Daily maximum SO_2 levels ranged from 40 to 1,283 $\mu g/m^3$ with a mean daily average of 188 $\mu g/m^3$ during the study period. These effects were observed for a 1 day lag period, and persisted even with NO_x and particles included in the model.

A cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES II) found no association between chronic exposure to SO_2 and decrements in lung function (Schwartz 1989). Levels of SO_2 during the study period ranged from a 10th percentile value of 0.006 ppm to a 90th percentile value of 0.019 ppm. Positive associations were found however for TSP, ozone and NO_2.

Xu et al (1991) examined the effects of air pollution on adult pulmonary function in Beijing, China. Respiratory diseases are the second leading cause of death in the overall population of China and air pollution is believed to be one of the most important risk factors (Xu et al 1991; Tao et al 1992). Higher levels of air pollutants have been found in northern cities compared with southern cities, and levels are higher during the winter than the summer. Indoor air pollution caused by cooking and heating with coal is considered to be a major contributor to the incidence of respiratory disease (Tao et al 1992). Xu et al found associations between both indoor and outdoor levels of TSP and SO_2 and reductions in FEV_1 and FVC. Annual mean concentrations of SO_2 in Beijing during the study period ranged from 18 to 128 $\mu g/m^3$. An increase in indoor SO_2 levels of 1$\mu g/m^3$ was associated with a 35.6 ml reduction in $FEV_{1.0}$ and a 131.4 ml reduction in FVC.

CONCLUSIONS

Epidemiological studies have shown significant associations between daily average SO_2 levels and mortality from respiratory and cardiovascular causes. Daily mean SO_2 levels at which these effects have been observed range from 30 to 636 $\mu g/m^3$. Increases in hospital admissions and emergency room visits for asthma, COPD and respiratory disease have also been associated with ambient

SO$_2$ levels. These associations were observed up to a 2 day lag period. Long-term exposure to SO$_2$ and SO$_4^{2-}$ has been associated with an increase in mortality from lung cancer and development of asthma and COPD. Increases in respiratory symptoms have also been associated with SO$_2$ levels.

TABLE 2

NS = not significant sorted in approximate order of ambient levels within each outcome group

Location and Period	SO$_2$ Levels observed	Other Pollutants in Model	Conclusion regarding SO$_2$ effect	Reference
Mortality				
Athens 1975-1982	Mean daily averages 62.4-126.5 µg/m^3 Max daily values 392-936µg/m^3	TSP	Respiratory causes ? adjustment	Katsouyanni et al., 1990
Cracow 1977-1989	daily average < 40µg/m^3 on 19% of days daily average > 200µg/m^3 on 6% of days	PM20	100 µg/m^3 increase associated with19% increase in respiratory mortality and 10% increase in circulatory mortality (significant independent effects)	Kryzanowski and Wojtyniak, 1991/1992.
Czech Republic 1986-1988 (cross-sectional)	average annual mean: 31.9µg/m^3 (lowest quintile 12.5, highest quintile 57.9)	TSP, Nox	neonatal mortality. Adjusted RRs (highest vs lowest quintile) is 3.91 (p = 0.06)for respiratory mortality. NS for all cause mortality	Bobak and Leon, 1992.
Steubenville	Mean 28.8 ppb 90th percentile 58 ppb	TSP	no independent effect of SO2 over the full year	Moolgavkar et al, 1995b.
Philadelphia 1973 to 1980	Mean daily average: 21 ppb 95th percentile: 46 ppb	TSP	total mortality increased 5% per 100 µg/m^3 increase in daily mean. However, association NS after adjustment for TSP	Schwartz and Dockery, 1992.
Philadelphia 1973-1988	Mean daily averages 15.7 to 25.4 ppb Max levels 100 to 156 ppb	TSP, ozone	adjusted RR per 100µg/m^3 1.19 Spring 1.14 Fall 1.21 Winter (all significant)	Moolgavkar et al., 1995a.
Athens 1987-1991	Mean daily average 51.3 µg/m^3 Max 361 µg/m^3	Black Smoke, CO	all cause mortality increased 12% per 100 µg/m^3 in daily mean. Remains significant after adjustment for others	Touloumi et al., 1996

Location and Period	SO$_2$ Levels observed	Other Pollutants in Model	Conclusion regarding SO$_2$ effect	Reference
Lyon 1985-1990	Mean daily average 46.8 µg/m^3 Maximum 635.7 µg/m^3	PM$_{13}$	unadjusted RR per 50 µg/m^3 increase is 1.22 for respiratory causes and 1.54 cardiovascular causes (both significant)	Zmirou et al., 1996
Athens 1984-1988	Mean daily average 44.9 µg/m^3		A 0.65% decrease in mortality per 10% decrease in daily average SO$_2$ Steeper slope at lower SO2 levels ? no adjustment	Touloumi et al., 1994
Barcelona 1985-1991	Mean daily average 41.2 µg/m^3 (range 2.2 to 160)	Black Smoke	unadjusted RR per 100 µg/m^3 1.13 total, respiratory and elderly 1.14 cardiovascular causes associations stronger for SO2 than for BS (but not adjusted for each other)	Sunyer et al., 1996.
Detroit	Mean 12 ppb 95th percentile 26.3 ppb ? daily average	TSP	strongest association observed for previous day in univariate model. However, no independent effect	Schwartz, 1991.
London 1987-1992	median daily average 31µg/m^3 Max. daily average 100µg/m^3	Black Smoke Ozone	significant association with all cause and respiratory mortality with a one day lag NS after adjustment	Anderson et al, 1996
London 1958-1972	not stated	Black Smoke	significant univariate association with all cause mortality but NS effect after adjustment for BS	Schwartz and Marcus, 1990
Sao Paulo	Mean daily average 6.5 ppb	PM$_{10}$, NOx$_x$, CO	Signif assoc in the elderly in univariate analysis. Not significant with adjustment	Saldiva et al., 1995
Hospital Admissions				
Cleveland	Mean 35 ppb	O$_3$, PM$_{10}$	RR 1.03 per 100 µg/m^3 for respiratory disease (not adjusted for other pollutants)	Schwartz, 1996
Birmingham, UK	Mean daily average 39.1µg/m^3 Maximum 126.3µg/m^3	Black Smoke	significant independent effect of weekly SO2 on asthma admissions in winter and all respiratory admissions in autumn	Walters et al., 1994.

A Review on Existing Health Data on Six Pollutants

Prepared by Dr Jonathon Streeton for the National Environment Protection Council

Location and Period	SO$_2$ Levels observed	Other Pollutants in Model	Conclusion regarding SO$_2$ effect	Reference
West Midlands, UK cross-sectional		smoke, NO2	no significant independent effect of SO2 on respiratory admissions	Walters, 1995
Helsinki	Daily averages 13-26 µg/m³	NO2, Ozone, TSP	asthma admissions: significant association in over 15 year olds ? adjusted for other pollutants	Ponka and Virtanen, 1996
Helsinki	3 year mean daily average 19.2 µg/m³	O₃, NO₂, NO, CO, TSP	Associations with asthma admissions ? adjusted for other confounders	Ponka, 1991
Emergency Room Visits				
Barcelona	24 hr averages 39-310 µg/m³ Annual average 56.5 µg/m³ 1 hour maximum values mean 142µg/m³ (range 14 to 720)	Black Smoke, CO	An increase of 2 visits per day per 100 µg/m³ (not adjusted for other pollutants)	Sunyer et al., 1991
Barcelona 1985-1986	Mean 24 hour average 49 µg/m³ winter 29 µg/m³ summer	Black Smoke	COPD attendances 25 µg/m³ increase in daily average associated with 6% increase in winter and 9% in summer (significant on high BS days, not adjusted for BS)	Sunyer et al., 1993
UK	Mean daily average 22µg/m³	Black Smoke, Ozone, NO₂	A 12% increase per 14 µg/m³ in daily average. (borderline significant, not adjusted for other pollutants)	Buchdahl et al., 1996.
Respiratory Symptoms and Lung Function:				
East Germany	Mean daily average 188 µg/m³ Daily maximum range 40 to 1,283 µg/m³	NO$_x$, particles	highest quartile vs lower three quartiles OR = 1.72 for the development of upper respiratory symptoms risk seen at high levels of SO2. (remained significant after adjustment for other pollutants)	Von Mutius et al., 1995.

A Review on Existing Health Data on Six Pollutants

Location and Period	SO$_2$ Levels observed	Other Pollutants in Model	Conclusion regarding SO$_2$ effect	Reference
Beijing, China	annual mean range 18 to 128μg/m^3	TSP	significant association with decreased FEV1 and FVC (no adjusted for other pollutant)	Xu, 1991
Steubenville	Daily averages 0-281 μg/m^3		-16 ml FVC -13 ml FEV$_{0.75}$ over given range of SO$_2$ concentrations	Dockery et al., 1982.
Havard Six Cities Study (cross-sectional, ecological)	Annual average range 3.4 to 68.3 μg/m^3	TSP, particulate SO$_4{}^{2-}$	association with cough (significant unadjusted)	Ware et al 1986
Havard Six Cities Study (cross-sectional, ecological)	Yearly average range 3.5 to 27.8 ppb	SO$_4{}^{2-}$, TSP, PM$_{15}$, and PM$_{2.5}$.	association with chronic cough, bronchitis, chest illness no association with lung function not adjusted for other pollutants	Dockery et al., 1989
USA (NHANES II) cross-sectional	10th centile 6ppb 90th centile 19ppb	TSP. Ozone, NO2	no association with decreased lung function	Schwartz, 1989
California		TSP	An 18% increase in developing symptoms of COPD at levels above 40ppb for 500 hours/yr	Euler et al., 1987.
Oporto, Portugal	Mean 23.9 μg/m^3 Maximum daily mean 83.5 μg/m^3	Black Smoke	Lower threshold of asthmatic children to other bronchospasm stimulus but no association with asthma attack rate	Queiros et al., 1990.

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