Review of the National Environment Protection (Ambient Air Quality) Measure

Discussion Paper Air Quality Standards

July 2010

Prepared for the National Environment Protection Council

NOTE

This Discussion Paper has been developed by a Project Team of government officers from Environmental Protection and Health portfolios, at the request of the National Environment Protection Council. The Paper is provided as a basis for discussion and does not necessarily reflect the views of NEPC Committee. The paper does not carry the endorsement of the National Environment Protection Council nor any member government.

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1. INTRODUCTION

1.1 National Environment Protection Council

The National Environment Protection Council (NEPC) is a national body with responsibility for making National Environment Protection Measures (NEPMs). As a statutory entity within the Environment Protection and Heritage Council (EPHC), its role is to harmonise environmental protection approaches across Australia. Appendix A provides contextual information on the NEPC and EPHC.

1.2 National Environment Protection Measures

A National Environment Protection Measure (NEPM) is legislation designed to protect particular aspects of the environment. A NEPM is similar to environmental protection policies existing in several states. It may have one or more goals, standards and protocols, and it may contain guidelines.

The NEPC Act requires that Council have regard to the Intergovernmental Agreement on the Environment (IGAE) 1992, when making NEPMs. A Schedule to the NEPC Act (1994) establishes the general provisions for the making of NEPMs, and as stated in the IGAE, the objectives of NEPMs are to ensure:

- that people enjoy the benefit of equivalent protection from air, water and soil pollution and from noise, wherever they live
- that decisions by businesses are not distorted and markets not fragmented by variations between jurisdictions in relation to the adoption or implementation of major environment protection measures.

The IGAE also requires consideration of the Precautionary Principle in the development of NEPMs.

1.3 The Ambient Air Quality NEPM

In 1998, NEPC made the Ambient Air Quality National Environment Protection Measure (AAQ NEPM) that set national ambient air quality standards to apply in all States and Territories and over land controlled by the Commonwealth. These standards cover six common pollutants—particles (PM_{10}), ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide and lead. The NEPM provides a nationally consistent framework for the monitoring and reporting of these six pollutants. This was the first time that national air quality standards had been set in Australia.

At the time of making the AAQ NEPM a number of 'future actions' were initiated to facilitate the review of the NEPM. In addition, other associated work was commenced which also provides information for the review of the NEPM. These future actions and associated work included preliminary reviews of particular pollutant standards and a number of research studies. Accordingly, the NEPM was varied in 2003 to incorporate advisory reporting standards for fine particles ($PM_{2.5}$) and preliminary work for a review of the ozone standards and standard for sulfur dioxide was completed in 2005. The Time-Activity Study was completed in 2004, and the Multi-city Mortality and Morbidity Study completed in 2006. The Children's Health and Air Pollution Study is currently being conducted and it is anticipated that the results of the study will be available for consideration if a variation to the NEPM is decided.

Although the AAQ NEPM deals only with ambient air quality, it is acknowledged that indoor air quality is also an important factor in the exposure of individuals to air pollution. However studies in Australia and overseas have shown that outdoor air pollution infiltrates indoors and can be a major driver of indoor air pollution levels. For some pollutants (e.g. ozone and sulfur dioxide which are highly reactive gases) the main exposure is outdoors. The AAQ NEPM focuses on ambient air pollution whereby monitoring can be undertaken and management actions implemented by jurisdictions.

Given the infiltration of outdoor air into the indoor environment, reductions in ambient air pollution levels will also lead to reductions in indoor air pollution.

1.4 Goal and desired environmental outcome of the AAQ NEPM

The AAQ NEPM interprets the objectives of the IGAE for equivalent protection as its national environment protection goal and desired environmental outcome.

The National Environment Protection Goal of the AAQ NEPM is "to achieve the National Environment Protection Standards as assessed in accordance with the monitoring protocol (Part 4) within 10 years from commencement to the extent specified in Schedule 2 column 5 of the AAQ NEPM." The desired environmental outcome of the AAQ NEPM is "ambient air quality that allows for the adequate protection of human health and well-being."

1.5 Review of the AAQ NEPM

When the AAQ NEPM was made there was a commitment to initiate a full review of the measure in 2005. The overall purpose of the NEPM review is to evaluate the performance of the current AAQ NEPM in achieving the desired environmental outcome, and to recommend to Council any required changes to the NEPM.

In April 2005 NEPC initiated this review with the development of an Issues Scoping Paper (ISP). The ISP sought input from key stakeholders on issues that needed to be considered through the review of the AAQ NEPM. The feedback from consultation on the ISP was used to fully scope the review process. In April 2006 NEPC approved the scope, budget and timeline for the review.

To inform the review of the AAQ NEPM, EPHC established the standard setting working group (SSWG) to develop a nationally agreed approach to the development of air quality standards in Australia. This group has been established as a partnership between the health and environment sectors and is jointly chaired by a EPH Standing Committee members who represent Victoria and the Australian Health Minister's Advisory Council. When NEPC approved the scope, budget and timeline for the review, they also endorsed incorporating the work of the SSWG as a formal part of the review of the AAQ NEPM.

1.6 Terms of reference for the review

Terms of Reference (TOR) for the review have been drafted based on the outcomes of consultation. The TOR are consistent with the generic clause that is now incorporated into NEPMs that outlines the requirements for a review of a NEPM. Such a clause was not included in the Ambient Air Quality NEPM when it was made. Submissions on the Issues Scoping Paper (ISP) supported terms of reference for the review that draw on this generic clause as well as on Section 15 of the *National Environmental Protection Council Act 1994*,

which sets out the factors that Council must take into account in making national environmental protection measures.

In light of the comments received the review of the Ambient Air NEPM will consider:

- the effectiveness of the Measure in achieving its desired environmental outcome, which is 'ambient air quality that allows for the adequate protection of human health and wellbeing'
- the effectiveness of the Measure in generating comparable, reliable information on the levels of air pollutants
- the environmental, economic and social impact of the measure, including unintended consequences
- the simplicity, efficiency and effectiveness of the administration of the measure, including the adequacy of its support mechanisms
- any regional environmental differences in Australia and the implications for the Measure
- the links between the Ambient Air Quality NEPM and other Government policies (including other NEPMs) and the potential for integration
- the need, if any, for varying the Measure, (in accordance with the Act) including:
    - whether any changes should be made to the Schedules
    - whether any changes should be made to improve the effectiveness of the
    - Measure in achieving the desired environmental outcome set out within it;
    - the potential costs and benefits of any proposed changes.

Consultation on the ISP also revealed the need for the review to examine international trends in approaches to air quality management and Australia's position in relation to these trends.

The review is being conducted in two stages. The first stage of the review focused on NEPM effectiveness, and monitoring and reporting protocols. This second stage of the review focuses on a review of the air quality standards. During the first stage of the review a Discussion Paper was released (June 2007) which sought input to the options for addressing issues of NEPM effectiveness, monitoring and reporting protocols contained in the NEPM.

1.7 Process of the review

The following lays out the progress and stages of the review to provide context for the role of this discussion paper in the review process.

1.7.1 Development and distribution of Issues Paper

The Issues Paper was developed in 2005 and stakeholder views sought to assist with the formulating of the proposal for the scope of the NEPM review. Submissions to the Issues Paper identified the areas of concerns and detailed the issues to be investigated in the review. From these submissions a review proposal was presented to NEPC in 2006 who initiated the review that same year.

1.7.2 Discussion Paper on NEPM framework, monitoring and reporting

During 2006-2007 the project team developed a Discussion Paper which examined the current framework of the NEPM, and its monitoring and reporting protocols. NEPC

released the discussion paper in 2007 for public consultation, inviting stakeholder submissions.

1.7.3 Discussion Paper on standards (this discussion paper)

This Discussion Paper deals with the standards in the NEPM and examines the health evidence to assess whether the current standards are still appropriate is the light of any new health evidence. Stakeholder comment is sought on the information presented in this paper.

1.7.4 Review report on findings of review and recommendations

Once submissions have been received and analysed, the project team will compile the AAQ NEPM review report for NEPC. The review report will draw from the information and submissions made on the two discussions papers and will present recommendations to NEPC in November 2010. At that time NEPC will also decide whether a proposal to vary the NEPM should be presented at its first meeting in 2011.

1.7.5 Cost benefit analysis

As part of the review, a preliminary cost benefit analysis (CBA) of possible changes to the AAQ NEPM is being conducted, to inform NEPC's decision on whether to proceed to a variation of the NEPM. If NEPC decides to proceed with a variation, a more detailed and comprehensive CBA and impact assessment would be conducted to identify and assess the economic and social impact on the community.

Costs of air pollution are typically estimated on the basis of health impacts and net benefits of changing standards are estimated as health costs avoided, less increased abatement costs. The rationale for a CBA approach is that community resources for health and the environment should be spent in a cost effective way; large expenditure for marginal benefits is not an outcome that is contemplated under a CBA approach

Each airshed is likely to require somewhat different policy responses so marginal abatement costs may vary from city to city. For example, Sydney would be likely to require more stringent measures to meet a possible tighter standard for ozone than other cities but the resulting health benefits would also be likely to be greater.

1.7.6 Emission reduction actions

- Closely linked to the review process, jurisdictions are working together under the EPHC to develop a set of national emission reduction actions that will improve air quality and help meet the existing NEPM and any potential variation to the NEPM. These will complement the air quality management strategies of individual jurisdictions. The feasibility of additional emission reduction actions at State and national level to meet the Measure will be also be undertaken to inform NEPC's decision on whether to proceed to a variation of the NEPM.

1.8 Purpose of this discussion paper

The purpose of this paper is to gain stakeholder and public views on the health evidence relating to air quality standards, to inform the development of recommendations to NEPC on initiating potential variations to the NEPM. Before making any changes to the NEPM, NEPC will consider the health evidence, stakeholder views and also the feasibility and the

costs and benefits of potential variations to the NEPM. This Discussion Paper focuses on the basis of deriving standards, the form of the standards, the selection of health outcomes on which the standards are focussed and how Australian air quality standards fit in relation to trends and practices overseas.

Chapter 2 discusses the role of air qualtiy standards in air quality management and the basis for the current standards. It also provides information of the "future actions" agreed by NEPC when the NEPM was made.

Chapter 3 reviews the new evidence of the health effects of each of the criteria pollutants. This section also reviews the health evidence for benzene and BaP which were raised during consultation in the first discussion paper.

Chapter 4 reviews the international trends in air quality standards and approaches.

Chaper 5 presents information of the form of standards and approaches and discusses options for the form of future standards.

2. AMBIENT AIR QUALTIY NEPM STANDARDS

2.1 Role of the NEPM standards in air quality management

A National Environment Protection Standard means a standard that consists of quantifiable characteristics of the environment against which environmental quality can be assessed. In other words, a standard provides a quantifiable target for ambient environmental quality.

The objective of the NEPM was to develop a set of nationally acceptable ambient air standards or 'quantifiable characteristics', which act as benchmarks against which the quality of ambient air can be assessed. The standards were designed to be measured at specifically nominated performance monitoring stations located to give an average representation of general air quality and of population exposure to the six main pollutants. The NEPM monitoring protocol does not apply to monitoring and controlling peak concentrations from major sources such as heavily trafficked roads and major industries. Monitoring of these major point sources is the responsibility of each individual jurisdiction, and consequently, is outside the scope of this NEPM. Of course, where monitoring at point sources is used to control pollutant emissions then this will also assist in meeting the standards at the NEPM nominated monitoring stations. The air quality standards in the AAQ NEPM drive jurisdictional air quality management actions to meet a nationally agreed benchmark.

2.2 Development of Ambient Air Quality NEPM Standards (1998)

In developing the standards for the AAQ NEPM a consultant was commissioned to conduct an independent review of the existing information on the health effects of the pollutants under consideration and make recommendations on the range of potential standards for each pollutant that would protect susceptible groups within the population. A technical review panel consisting of Government, industry and community health and medical experts was established to review the consultant's reports and make independent recommendations on possible standards.

The project team involved in developing the NEPM reviewed international air quality standards and guidelines and compared those against those recommended in the health review and by the technical review panel.

An assessment was undertaken on existing air quality in Australian cities and the achievability of the range of standards within the 10-year timeframe established for compliance with the NEPM standards. An assessment of the costs and benefits, including the avoided health costs associated with reducing air pollution levels to meet the standards, was undertaken. Based on this analysis—consideration of health effects, achievability and costs and benefits associated with improvements in air quality to meet the standards—a final set of standards was recommended. These standards were released for public consultation and based on the outcomes of the consultative process and consideration of what could be achieved within 10-years of the making of the NEPM a final set of standards were recommended and ultimately adopted by NEPC.

2.3 Pollutants included and basis for the standards

The AAQ NEPM contains standards for the six common pollutants—nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), ozone (O_3), lead (Pb), and particles as

PM_{10}. The NEPM was varied in 2003 to include advisory reporting standards for particles as $PM_{2.5}$. These pollutants were selected as they are widely spread in the air environment and arise from many sources. They are considered to largely describe ambient air quality.

In setting air quality standards NEPC examined the latest health related air pollution research from around the world, examined the information available on the state of our major airsheds and, taking into account the technology that was readily available, assessed what level of air quality could be achieved within ten years, without significant social and economic disturbance. These standards are based on the best information on the health effects of these pollutants that was available at the time of making the NEPM. The resulting standards were considered to be a first step in establishing a consistent approach to managing air quality around Australia, with the ultimate aim of providing equivalent protection to all Australians wherever they live.

A report was commissioned on the state of knowledge of the human health effects of the six pollutants, with the consultant tasked to identify adverse health impacts on both the general population and on any susceptible subgroups. The consultancy also required the identification of a 'dose response relationship' for each pollutant, and the determination of any concentration 'thresholds' for the effect of the pollutant on human health. The outcome of the consultancy was a series of recommendations on the ambient levels (or pollution concentration ranges) that would provide protection from the lowest observable adverse effects on susceptible sub-groups in the population. The health research cited was largely epidemiological studies supplemented by laboratory studies on individual or groups of subjects. The report was internationally peer reviewed and its conclusions supported.

A number of issues arising from the health review included the use of chamber studies in determining appropriate ambient air quality levels, difficulties in separating the health effects of individual pollutants from the effect of a mixture of the pollutants, the interactions between allergens and pollutants, and the complexity associated with determining unambiguous dose-response relationships. An additional challenge was the absence of a threshold for adverse health effects for some pollutants—in particular ozone and PM_{10}.

Advice was subsequently sought from a Technical Review Panel on whether or not the consultant had taken all the relevant information into account, and the Panel was asked, on the basis of the information in the report, to make recommendations for acceptable ambient levels for each pollutant. These recommendations were based solely on the protection of human health. While there was not complete consensus on the concentrations of concern there was a high degree of agreement. The technical review panel consisted of Government health representatives as well as representatives of industry and the community.

As it was considered likely that in a number of instances the starting point for the development of a standard would need to be revised upwards, as other costs and benefits were considered, a range of possible standards was developed. The recommended standards identified by the Technical Review Panel were taken as a starting point, and were added to by considering the relevance (in terms of recent health studies) of any pre-existing standards/guidelines (such as the NHMRC and WHO guidelines). Where the standards were relevant, they were included in the range, and where there was considerable divergence between the two levels, an intermediate level was included.

Following a rigorous review of all the available information, the main inputs to the assessment process were identified as the outcomes of the health review, exposure

assessment, the examination of the air quality management or 'control' options and their associated costs for achieving any proposed standards, and consideration of the benefits, typically in terms of avoided health costs, associated with each of the standards.

A preferred set of standards was determined from the range of options by using these other inputs and by considering the pollutants in three separate groups (see Table 2.1). This grouping was based on the understanding of the health effects that were available at that time and reflects decisions made based on that information as to how these pollutants should be considered. Section 3 discusses the current thinking on the existence of thresholds for these pollutants.

Table 2.1 Identification of thresholds for pollutants in NEPM standards*

Health effects threshold	Pollutant
Identified threshold	Sulfur dioxide Carbon monoxide
Apparent threshold	Nitrogen dioxide Lead
No identified threshold	Ozone Particles

*Note: This grouping reflects the decisions as to how these pollutants should be considered based on the health effects available at the time of making the AAQ NEPM.

For those pollutants with identified or apparent thresholds, the option that related to the lowest (or no) observed adverse effect level (i.e. the LOAEL or NOAEL) was preferentially selected for further assessment. Careful consideration was given to ensuring that the research data supporting the identification of this level was robust and generally supported by other researchers in the area. For pollutants with no identified threshold the lowest option, which would minimise the likelihood of adverse impacts, was preferentially selected for further assessment.

Uncertainty/safety factors are often used in standard setting to account for uncertainty in the data unpinning the standard. This uncertainty can arise from a range of sources including:

- extrapolation from animals to humans
- extrapolation from high exposure scenarios (e.g. occupational settings) to lower environmental exposures
- quality and size of epidemiological or toxicological data used for dose-response data
- extrapolation from healthy population to sensitive groups
- quality and quantity of exposure data (e.g. available air monitoring data).

As a general principle uncertainty (or safety) factors were not used in the development of the standards in the AAQ NEPM. The exception to this was where there was evidence for the existence of a threshold. Uncertainty (or safety) factors were then applied to account for differences between the study population and sensitive groups that exist within the broader population. The greater the uncertainty about the existence of a threshold the larger the uncertainty factor applied.

The available health, economic, social, technological and environmental data were examined to determine the preferred standards for each pollutant. Following public comment these were then reviewed and amended where appropriate. Available air monitoring data were examined to determine levels and trends for each of the pollutants within each airshed. Following a review of the technologies readily available for the control of emissions, an assessment was made of the improvements that could be achieved in air quality around the country over the ten-year period after making the NEPM. A set of standards and a ten-year goal in relation to meeting them was then proposed. Following public comment these were reviewed and amended where appropriate. The standards, therefore, represent a high degree of consensus among leading health professionals, varied to reflect what is realistically achievable in Australia.

Some of the proposed standards raised particular concerns during the public consultation. Some industry representatives queried the need for a short-term (1 hour) sulfur dioxide standard. However, such a standard already existed in most jurisdictions either in a formal sense or by adoption of the NHMRC goals. Environmental/community groups recommended that a 10 minute standard be introduced. The health review recommended a short-term (10 minute) standard and this was generally supported by the Technical Review Panel. However, having reviewed the industry position, along with the health expert and environmental groups comments, and the capacity to validly monitor compliance with a 10 minute standard, NEPC decided that the 1 hour standard for sulfur dioxide should be adopted, and agreed to a review of the practicability of developing a 10 minute sulfur dioxide standard within 5 years (see Section 2.5).

Particles were clearly also an area of major concern and one where the science continues to evolve. NEPC made clear its commitment to keeping this issue under review, collecting more Australian based data and revisiting the question of appropriate size fraction with a review of the need to introduce a $PM_{2.5}$ standard which commenced in 2001 (see Section 2.6).

Lead was a significant issue for both industry and community representatives. NEPC recognised that actions already taken at both the national level and within individual jurisdictions had significantly reduced lead concentrations in urban air and would continue to do so for some years. The standard proposed was met in most locations at the time of making the NEPM. Regional centres with stationary source or historical problems were considered to be able to meet the ten-year goal on the information available at that time. Given that lead has no known beneficial biological role, the standard was considered to represent a useful benchmark for the future. Subsequent removal of lead from petrol has reduced lead levels in urban air sheds to below detectable levels. The final standards and associated goals adopted in the NEPM are listed in Table 2.2.

Table 2.2 NEPM Standards and Goal

	Pollutant	Averaging period	Maximum concentration	Goal within 10 years maximum allowable exceedences
1	Carbon monoxide	8 hours	9.0ppm	1 day a year
2	Nitrogen dioxide	1 hour 1 year	0.12ppm 0.03ppm	1 day a year none
3	Photochemical oxidants (as ozone)	1 hour 4 hours	0.10ppm 0.08ppm	1 day a year 1 day a year
4	Sulfur dioxide	1 hour 1 day 1 year	0.20ppm 0.08ppm 0.02ppm	1 day a year 1 day a year none
5	Lead	1 year	0.50µg/m^3	none
6	Particles as PM_{10}	1 day	50µg/m^3	5 days a year

2.4 Health impacts considered

At the time of making the NEPM the majority of available health data was data from overseas, in particular the US and Europe. Data from Australian studies was very limited and in some cases non-existent. Therefore the air quality standards adopted in the AAQ NEPM were based on information obtained from overseas epidemiological and controlled exposure studies. This was a significant point of debate in the development of the standards with some stakeholders raising concerns that the results of overseas studies may not be transferable to Australia. The main concerns related to differences in pollution levels and mix as well as possible variability in the susceptibility of the population (e.g. higher asthma rates in Australia compared to the US). The following sections provide a brief overview of the health effects considered as the basis of the standards adopted in the AAQ NEPM.

2.4.1 Carbon monoxide

The adverse health effects of carbon monoxide are linked with carboxyhaemoglobin (COHb) in blood. The health effects considered in the development of the standards are summarised in Table 2.3.

Table 2.3 Adverse health effects from exposure to carbon monoxide

Health effects	LOAEL (% COHb)	NOAEL (% COHb)
Cardiovascular Effects—Healthy Adults:		
Decreased O_2 Uptake Decreased Work Capacity (Maximal Exercise)	5.0–5.5%	< 5.0%
Significant Decrease in Work Time	3.3–4.2%	< 3.0%
Strenuous Exercise—Maximal O_2 Consumption	7–20%	
Cardiovascular Effects—People with Ischaemic Heart Disease:		
Decreased Exercise Capacity at Onset of Angina, Increased Duration of Angina	2.9–4.5%	2.5%
Neuro-behavioural 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 Sensori-motor Tasks	5.0–17%	<5.0%
Foetal Effects		
Reduced Birth Weight (Non Smoking Mothers)	2.0–7.0%	<2.0%

There is a linear dose response relationship between CO and Carboxyhaemoglobin (COHb) that allows predictable levels of COHb for a given ambient concentration of CO, for a given duration of exposure, and at a given level of rest or exercise. Although the relationship between ambient levels of CO and the resultant COHb levels is approximately linear in the region of ambient air concentrations, it is quite 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. Reduced birth weight and delays in foetal and neonatal development at exposure levels of COHb between 2 and 7% provide a NOAEL below 2%.

Groups within the population that were considered to be most susceptible to the effects of CO were people with cardiovascular disease, in particular the elderly with ischaemic heart disease. Advice from the health consultant and technical review panel was that achieving ambient levels of CO that did not lead to COHb levels above 2.5% averaged over 8 hours would provide protection for most of the population. An uncertainty factor of 1.5 was applied to the resultant concentration to protect the more susceptible groups. The resulting range of standards considered for CO was:

Health Review Study	*8 hour standard, 9 to 10ppm*
Technical Review Panel	*8 hour standard, 9 to 10ppm*
NHMRC (1984)	*8 hour goal, 9ppm*

The range recommended was quite small for CO with a majority support for an 8 hour standard of 9ppm which was adopted as the standard.

2.4.2 Nitrogen dioxide

A variety of health effects were identified as being associated with exposure to NO_2. Decreases in lung function and an increased incidence in respiratory illness had been noted in the general population and particularly in children. Asthmatics, the elderly and people with existing cardiovascular and respiratory disease are particularly susceptible to the effects of NO_2. Increases in hospital admissions and emergency room visits for respiratory and cardiovascular disease and asthma had also been linked with NO_2 exposure. There was also some evidence of increases in mortality due to exposure to NO_2. Although decreased lung function and increases in respiratory illness may not be as serious as some of the other health outcomes, they may impact significantly on the quality of life that an individual experiences. The health impacts depend significantly on both the duration of exposure as well as the concentration of NO_2 to which they are exposed.

The most susceptible groups within the population to exposure to NO_2 were identified as:

- people with asthma
- people with existing respiratory disease
- children.

On the basis of advice from the health consultant and technical review panel NEPC considered that achieving a standard for NO_2 of 0.12ppm averaged over a one hour period would provide a high level of protection for asthmatics and people with existing respiratory disease. The standard was consistent with the recommendations of the Health Technical Review Panel. It was tighter than the NHMRC goal for NO_2 of 0.16ppm averaged over a one-hour period that was in existence at that time (NHMRC air quality goals have subsequently been rescinded). A number of studies and reviews indicated that the NHMRC goal for NO_2 of 0.16ppm averaged over 1 hour was not sufficient to protect asthmatics and people with lung diseases and a lower standard was desirable.

In addition, based on advice from the health consultant and technical review panel NEPC considered that achieving a standard for NO_2 of 0.03ppm annual average would provide a high level of protection to children from increased risk of respiratory illness. The range of standards considered for NO_2 was:

Health Review Study	*1 hour standard, 0.10–0.15, annual average 0.03ppm*
Technical Review Panel	*1 hour standard, 0.12, annual average 0.03ppm*
NHMRC (1981)	*1 hour standard, 0.16ppm*

The range recommended for NO_2 was from 0.10ppm to 0.15ppm one hour average (except for the existing NHMRC goal) with a majority support for a standard of 0.12ppm one hour and 0.03ppm for annual. These standards were adopted in the NEPM.

2.4.3 Ozone

The health effects considered in the development of the standards for ozone are summarised in Table 2.4.

Table 2.4 Summary of health response to ozone exposure

Health Effect	Ozone Concentration (ppm)	Exposure Duration
Epidemiological Studies		
Reduced lung function (farm workers)	> 0.085	summer months whole day
Mortality (2.5% increase per 0.01ppm)	0.10 - 0.16	summer months
Reduced lung function in children, adolescents, and adults Exacerbations of asthma Respiratory symptoms	> 0.12 (daily 1 hour maximum)	days–weeks
Controlled Exposure Studies		
Reduced lung function	≥ 0.08	6.6 hours
Increased airways responsiveness	>0.1	1–3 hours
Airway inflammation	>0.1	1–3 hours

Health effects associated with exposure to ozone depend on the concentration and duration of the exposure. At the time of making the AAQ NEPM, health effects identified from exposure to ozone ranged from minor changes in lung function and increased symptoms consistent with airway irritation to more serious effects that lead to an increase in hospital admissions and emergency room visits for respiratory and cardiovascular disease. There was evidence of a small increase in mortality from respiratory and cardiovascular causes, especially in the elderly. Symptoms identified that may occur with exposure to O_3 included cough and chest pain on inspiration that, although not life threatening, may affect the quality of a persons life. Exercise was found to enhance the effects of ozone on lung function. Lung clearance mechanisms were also affected by exposure to ozone. Sensitive subgroups included the elderly and asthmatics.

The health effects identified were correlated with both daily 1 hr maximum and 8 hr maximum O_3 levels with the strongest effects observed with a 1-day lag. The effects on lung function and airway responsiveness had also been observed in controlled exposure studies in both human and animal studies. Results of bronchoalveolar lavage (BAL) showed that the observed response may be due to an inflammatory process. No association between spirometric responses, e.g. FEV_1, and BAL inflammatory end points had been observed. The observed effects appeared to be greater on asthmatics than on healthy subjects. Ozone has also been found to increase bronchial allergen responsiveness in sensitive groups.

The health consultant and technical review panel considered that there was consistent evidence to suggest that there were specific subgroups in the population, in particular asthmatics, which were more susceptible to the adverse health effects from ozone exposure, and variability in individual susceptibility is large. The interaction of ozone with other

pollutants, in particular, the enhancement of the effects of ozone as a result of prior or concurrent exposure to particles, nitrogen dioxide, airborne allergens, and sulfur dioxide, and conversely, for people with asthma, sensitisation to other agents by exposure to ozone was also noted. Controlled chamber studies supported the findings of the population based epidemiological studies.

No threshold exposure level was identified for ozone and it was not possible to define either a No Observable Adverse Effect Level (NOAEL) or a Lowest Observed Adverse Effect Level (LOAEL). The ozone standards were selected on the basis of providing health protection for the majority of the population including susceptible groups (e.g. the elderly and asthmatics), being technically achievable, and providing comparable costs and benefits within the limitations of the analysis. The standards were consistent with the NHMRC guidelines that existed at that time and were being used by most jurisdictions.

The health effects of ozone considered in setting the standards were:

- increases in hospital admissions and emergency room visits for respiratory and cardiovascular disease
- decreases in lung function, increases in respiratory symptoms such as cough and chest pain on inspiration
- increased mortality.

Tighter standards recommended by the Health Technical Review Panel (0.08ppm 1 hour average and 0.06ppm 8 hour average), and supported by health departments and health professionals were recommended to jurisdictions as a long-term goal but were assessed as not practicably achievable within the ten-year timeframe for attainment. This was mainly due to motor vehicle replacement rates that were estimated at 17 years for full turnover.

The selection of a 4-hour standard as opposed to an 8-hour standard was based on providing a standard that was as close in stringency to the Technical Review Panel recommendation as was technically achievable, and was also statistically compatible with the 1 hour standard. The NEPC made a commitment to review the ozone standards in 5 years (see Section 2.5). The range of standards considered for O_3 was as follows:

Health Review Study	*1 hour standard, 0.09ppm; 8 hour 0.05ppm*
Technical Review Panel	*1 hour standard, 0.08ppm; 8 hour 0.06ppm*
NHMRC (1995)	*1 hour standard, 0.10ppm; 4 hour 0.08ppm*

The range recommended for O_3 was from 0.08ppm to 0.09ppm one hour average (except for the existing NHMRC goal) with an 8 hour standard ranging from 0.05 to 0.06ppm. Based on information available at the time of making the NEPM, it was considered that these objectives would be very difficult to achieve in Melbourne and Sydney, and possibly Brisbane and Perth in the ten-year time frame for attainment of the standards. Taking note of the impracticability of meeting the recommendations of the health review and Technical Review Panel in the ten-year timescale it was concluded that the NHMRC's goals that were in existence at that time be adopted. It was acknowledged that there may be demonstrable health effects at the standard.

2.4.4 Sulfur dioxide

Both long and short-term health effects were considered in the development of the standards for SO_2. Exposure to SO_2 results in the development of an acute irritant response

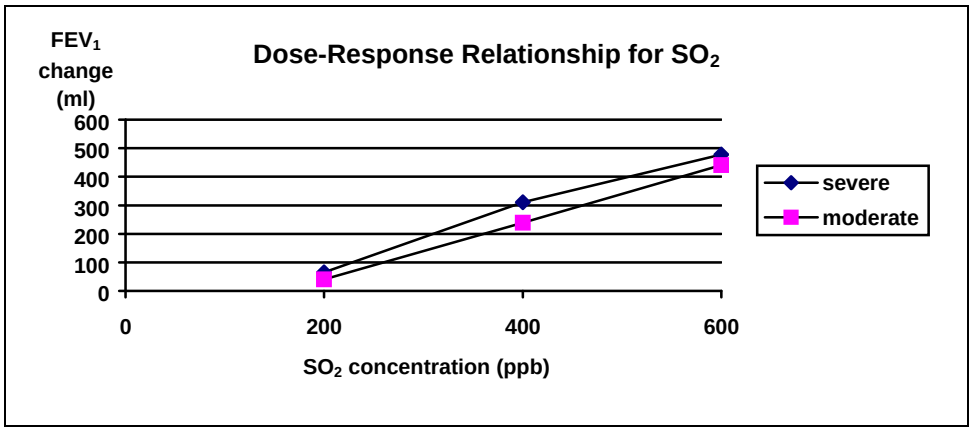
initially in the upper airways which leads to coughing, wheezing, sputum production, increased incidence of respiratory infections and aggravation of asthma and chronic obstructive airways disease (COPD). The impacts from these effects can be mild, such as an irritant cough through to more serious impacts such as increases in mortality and hospital admissions for respiratory disease and asthma. Asthmatics were considered to be particularly susceptible to SO_2 and respond very quickly (10–15 mins) to exposure even at low levels. The severity of the response depends on the concentration of SO_2 and the duration of the exposure.

The reviews of the health effects of SO_2 by WHO (1996) and Streeton (1997) were used to inform the setting of the standards. The only route of exposure of interest with regard to the health effects of SO_2 was considered to be inhalation. SO_2 acts directly on the upper airways (i.e. nose, throat, trachea and major bronchi) initially, producing rapid responses in minutes. It achieves maximum effect in 10 to 15 minutes, particularly in those individuals with significant airway reactivity such as asthmatics and those suffering similar bronchospastic conditions. A wide range of sensitivity is evident in both healthy and susceptible groups such as asthmatics, the latter being the most sensitive to irritants.

The results of population based epidemiological studies had shown associations between increases in SO_2 levels and increases in mortality, hospital admissions for asthma and respiratory disease, and increases in respiratory symptoms. In many instances it was difficult to separate the adverse effects resulting from exposure to SO_2 from those resulting from concurrent exposure to mixtures including other known irritant pollutants such as NO_2, ozone and, in particular, respirable particles. Results of controlled exposure studies supported the epidemiological findings with respect to exacerbation of asthma, increases in respiratory symptoms and decreases in lung function.

In developing protective ranges as part of standards both epidemiological and chamber studies were relevant. The former provide details of the effects of "real world" response, while the latter are the source of data on the minimum dose that produces an adverse effect, particularly in susceptible subjects. Figure 2.1 shows the dose-response function that was used with respect to changes in FEV_1 in asthmatics with exposure to SO_2.

Figure 2.1 Change in mean FEV_1 with increasing concentrations of SO_2



(15 minute duration) with exercise (after subtracting the effect of exercise alone) in patients with moderate and severe asthma (reproduced from WHO 1996)

The dose-response relationship for short term (15 minute) exposure to SO_2 shown in Figure 2.1 was interpreted as indicating a possible threshold for adverse effects at 0.2ppm for both moderate and severe asthmatics and a 10% reduction in FEV1 at 0.4ppm. In addition the results of exposure appear to be largely independent of the severity of the asthma. The evidence indicated that there was little significant difference in observed responses to SO_2 exposure, for exposure duration of 15 minutes and exposure duration of up to several hours. The response occurs quickly and appeared to alter little with recurrent exposure, even after more than one hour. Asthmatics were considered to be the most sensitive group to exposure to SO_2 and the standards were developed to protect against bronchospasm in this group. The range of standards considered for SO_2 was:

Health Review Study	10min, 0.175ppm; 24 hour, 0.04ppm; annual 0.02ppm
Technical Review Panel	10min, 0.12ppm; 24 hour, 0.04ppm; annual 0.02ppm
NHMRC (1995)	10min goal 0.25ppm; 1 hour, 0.20ppm; annual 0.02ppm

The range recommended for SO_2 is from 0.12ppm to 0.175ppm ten minute average (except for the existing NHMRC goal) no one hour standard was recommended and 0.04ppm 24 hour average and 0.02ppm as an annual.

Relevant exposure periods were considered in evaluating each set of standards for the protection of the susceptible population viz, short term (of the order of 10–15 minutes), medium term (24 hours) and long term (annual). The consultant recommended a set of standards covering the three exposure periods. The NHMRC goals that were in existence at that time for SO_2 provided guidance for human health protection at two levels of exposure, short term (10 minutes and one hour) and long term (annual). The Technical Review Panel recommendation of three exposure periods was also considered in developing the NEPM standards.

Significant costs to control SO_2 emissions meant that the more stringent objectives recommended by the Health Review were not seen to be achievable in all locations in the 10 year timeframe for compliance with the standards. It was concluded that the NHMRC's goals be adopted except for the 10 minute goal. A 10 minute standard was not set because of the inconsistency that would be evident in the monitoring and reporting protocols for SO_2 compared to the other pollutants. In addition to the 1–hour and annual NHMRC goals, a 24–hour standard was also set. The 24–hour objective was based on epidemiological evidence that sensitive groups within the population could develop respiratory symptoms at SO_2 concentrations above 0.087ppm. The adopted value of 0.08ppm was also considered to be achievable within the 10-year timeframe for compliance with the NEPM standards.

Jurisdictional data indicated that the proposed SO_2 one hour standard was met throughout Australia except close to some point sources, notably Mount Isa and Kalgoorlie which are subject to specific jurisdictional legislation. In most areas, SO_2 levels were also below the objectives recommended by the Health Review. The standards for sulfur dioxide are:

0.20ppm averaged over a one hour period
0.08ppm averaged over a one day period
0.02ppm averaged over a one year period.

Achieving the standard for SO_2 of 0.20ppm averaged over a one-hour period was considered to provide protection from increased risk of breathing difficulties for the bulk of the susceptible population. The standard was consistent with the NHMRC goal that existed at the time of making the NEPM.

2.4.5 Lead

Lead is absorbed after being inhaled or ingested. It can result in a wide range of adverse health effects depending on the level and duration of exposure. Absorbed lead is distributed among the soft tissues (blood, liver, kidneys, brain etc) and mineralising systems such as teeth and bone. The health impacts range from increased blood pressure in adult males, effects on central nervous system, effects on both the male and female reproductive systems, anaemia to pre-term deliveries and reduced birth weight. The most well known impacts of lead exposure in children are reductions in learning ability and IQ.

Absorbed lead is distributed among the soft tissues (blood, liver, kidneys, brain etc) and mineralising systems such as teeth and bone. Bones form the major lead storage site in the body, and lead accumulates in the bones over a person's lifetime (WHO, 1995b). Because of retention of lead in bone, conditions associated with increased bone catabolism may lead to increased circulating blood lead even when environmental exposures have been reduced or eliminated (Streeton, 1997). The concentration of lead in whole blood was considered to be the best available surrogate for cumulative exposure, and surveys of blood lead concentration have come to be regarded as measuring community exposure (Donovan *et al*, 1996). The concentration of lead in blood is usually expressed in micrograms per decilitre (μg/dL). The health effects considered through the development of the standards for lead are summarised in Table 2.5.

Table 2.5 Summary of lowest observed lead-induced health effects

Blood lead level	Lowest observed health effects	
(µg/dL)	Adults	Children and/or foetuses
> 100	Encephalopathic signs and symptoms	
> 80	Anaemia	Children: Encephalopathic signs and symptoms, chronic nephropathy (e.g. aminoaciduria)
> 70	Clinically evident peripheral neuropathy	Children: Colic and gastrointestinal symptoms
> 60	Female reproductive effects. Central nervous system symptoms (ie sleep disturbances, mood changes, memory and concentration problems, headaches)	
> 50	Decreased haemoglobin production, decreased performance on neuro-behavioural tests, altered testicular function, gastrointestinal problems (i.e. abdominal pain, constipation, diarrhoea, nausea, anorexia)	Children: Peripheral neuropathy
> 40	Decreased peripheral nerve conduction, chronic nephropathy	Children: reduced haemoglobin synthesis and Vitamin D metabolism
> 25	Elevated erythrocyte protoporphyrin levels in males	
15–25	Elevated erythrocyte protoporphyrin levels in females	
> 10	Elevated blood pressure (males aged 40–59 years)	Foetus: Pre-term delivery, impaired learning, reduced birth weight, impaired mental ability
≤ 10		Children: Both the level of concern and the lowest observed adverse effect level for the effects of lead on intelligence have been determined to be 10µg/dL.

Source: Streeton, 1997 (adapted from CDC, 1992).

Foetuses, babies and children (especially those below the age of 4 years) were considered to be more susceptible to the adverse effects of lead exposure than adults. This is due to their smaller body size (children eat and drink more per unit of body weight than adults, so their relative lead intake is increased); higher rates of gastrointestinal absorption (approximately 50% compared with 10% in adults); greater prevalence of nutritional deficiencies, such as iron and Vitamin D, which enhance absorption of lead; incompletely developed nervous systems (neurological effects of lead occur at lower thresholds than in adults); and higher rates of growth (WHO, 1995b; Streeton, 1997).

Children up to the age of 4–6 years are also considered to be a group at increased risk of exposure due to a range of behavioural characteristics. These include the greater amount of time they spend outdoors playing, hand to mouth behaviours (such as thumb sucking) and possibly pica. Pica is the compulsive, habitual consumption of non-food items, and where these include dust and paint chips, lead consumption can be significantly increased. Much of the lead poisoning caused by lead based paint has been found to occur because children actively eat paint chips (US EPA, 1986).

Attention had focused on children as a risk group for central nervous system (CNS) effects, at increasingly lower levels of exposure. As a global measure of CNS-functioning, intelligence quotient (IQ) had received particular attention in such studies. Analyses had consistently shown that a blood lead increase from 10µg/dL to 20µg/dL was likely to be associated with an IQ drop of 1–3 points (Schwartz, 1994; Pocock *et al*, 1994; WHO, 1995b). At blood lead levels greater than 25µg/dL this relationship may differ (Streeton, 1997).

Existing epidemiological studies did not provide definitive evidence of a threshold (Donovan *et al*, 1996). The research suggested that below a blood lead level range of 10-15µg/dL there was increasing uncertainty attached to the identified effects (WHO, 1995b).

Lead is foetotoxic. Since the placenta is not an effective biological barrier to lead, pregnant women were considered to represent a second group at increased risk because of exposure of the foetus to lead (WHO, 1995b). It was noted that it is not pregnant women *per se* who are at increased risk, but rather the foetuses. Umbilical cord studies involving mother-child pairs had repeatedly shown a correlation between maternal and foetal blood lead levels (US EPA, 1986). In some studies on pregnant women, blood lead levels above 15µg/dL had been associated with premature birth and low birth weight babies (Streeton, 1997). The adverse effects of very high lead concentrations in maternal blood on pregnancy outcome had been well documented and generally undisputed (Baghurst *et al*, 1987).

Other adverse health effects which have been associated with exposure to lead and considered in the development of the standard for lead include: premature deaths in adults, hypertension and coronary heart disease and other cardiovascular diseases, reproductive effects in women, and foetal effects from maternal exposure (including diminished IQ) and other neurological and metabolic effects. The standard for lead is based on achieving a blood lead level of less than 10µg/dL. This was considered to be protective of all Australians. The range of standards considered for lead was:

Health Review Study	0.3–0.5µg/m^3, 3 month / annual average
Technical Review Panel	0.5µg/m^3, 3 month average
Intermediate value	1.0µg/m^3, 3 month average
NHMRC (1979)	1.5µg /m^3, 3 month average

In view of the small increase in indicative avoided health costs between 0.5µg/m^3 and 0.3µg/m^3, the debate regarding the blood lead IQ loss threshold, blood lead correlation with lead in air, and the declining lead in air levels, it was concluded by NEPC that the recommendations of the Technical Review Panel and Health Consultant for an ambient air quality standard of 0.5µg/m^3, but averaged over a one year period, was appropriate for lead. Hence the standard for lead is: 0.5µg/m^3 averaged over a one-year period, reported as a fraction of TSP (total suspended particles).

2.4.6 Particles

The major health impacts associated with particles and considered in the development of the standard are:

- increased mortality
- aggravation of existing respiratory and cardiovascular disease
- increased hospital admissions and emergency department visits
- altered lung clearance and other host defence mechanisms
- respiratory mechanics and symptoms

It was also acknowledged that the effects summarised above could lead to a range of impacts such school absences, work loss days, and restricted activity days. Particles for which the evidence was greatest at that time of developing the standards were those that have an aerodynamic diameter less than 10μm, PM_{10}. It was also acknowledged that $PM_{2.5}$ may be even more important with respect to adverse health effects but that data, both health and air monitoring data was limited at that time. All particles irrespective of their origin appeared to cause adverse health impacts. Both short-term exposures to PM_{10} and long-term exposures to lower levels had been associated with health impacts. The dose-response relationships considered in the development of the standard for PM_{10} are summarised in Table 2.6.

Table 2.6 Summary of short-term exposure-response relationships of PM_{10} with different health effect indicators

	Percentage change in health indicator per 10 μg/m³ increase in PM_{10}
Daily Mortality (all cause)	1.0[a]
Respiratory Deaths	3.4[a]
Cardiovascular Deaths	1.4[a]
Hospital Admissions	
Respiratory Disease	1.96[b]
COPD	3.26[b]
Pneumonia	1.42[b]
Heart Disease	0.4[c]
Exacerbation of Asthma	3.0[a]
Increase in Respiratory Symptoms	
Lower Respiratory	3.0[a]
Upper Respiratory	0.7[a]
Cough	1.2[a]

[a] Dockery and Pope, (1994); [b] Abt. Associates, (1996); [c] Schwartz and Morris, (1995)

From the health reviews it was clear that there are subgroups within the population that are clearly more sensitive to PM_{10} exposure. These subgroups include the elderly and those individuals suffering from pre-existing heart or lung disease. There was also evidence to suggest that young children may be more sensitive, leading to an increased frequency of respiratory tract infections, coughing, and wheezing.

Statistical evidence suggested that the observed adverse health effects of PM_{10} appeared to occur independently of the presence of other pollutants such as ozone, nitrogen dioxide, and probably sulfur dioxide, although the reverse did not apply. There was evidence to suggest

that PM_{10} impacted significantly as a major confounder on the observed responses to other pollutants, however there was no satisfactory evidence that the effects of PM_{10} were influenced by other pollutants.

Based on epidemiological data, the health consultant and technical review panel concluded that there was no evidence of a threshold for the effects of exposure to PM_{10} on health. Further there was no available evidence to suggest that exposure to high particle concentrations for brief periods were more harmful than relatively constant low level concentrations. It was considered that further research was required before any useful progress could be made towards establishing air quality objectives based on short-term exposures less than 24 hours.

It was concluded that the evidence of particle related effects from epidemiological studies was fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several indices of particles. The indices that had been most consistently associated with health endpoints are PM_{10}, $PM_{2.5}$ and sulfate. Less consistent relationships had been observed for TSP, strong acidity (H^+), and coarse PM (PM_{10}- $PM_{2.5}$).

The reviews concluded that adverse health effects were associated with PM_{10} or $PM_{2.5}$ as opposed to total suspended particles and that there was no discernible threshold below which no adverse health effects occur. It was identified that there was a strong association between mortality and increased exposure to particles, to the extent of a 1% increase in premature mortality with every 10µg/m^3 increase in PM_{10}. The range of standards considered for particles was:

Health Review Study	PM_{10}: 50µg/m^3, 1 day average $PM_{2.5}$: 20 to 25µg/m^3, 1 day average
Technical Review Panel	PM_{10}: 50µg/m^3, 1 day average $PM_{2.5}$: 25µg/m^3, 1 day average
NHMRC	No goal

The range recommended was quite small with a majority support for a 1 day standard of 50µg/m^3 for PM_{10} and a 25µg/m^3 standard for $PM_{2.5}$. The Technical Review Panel recommended that this be reviewed in five years time. An attempt was made to provide an illustrative example of potential cost savings to the health system using estimates of increased mortality derived from a study conducted in Sydney (Morgan *et al*., 1998) and health cost data taken from the USEPA (1997). The mortality estimates were extrapolated for the whole of Australia assuming that PM_{10} levels in other parts of Australia (outside capital cities) were half those experienced in Sydney. It was also assumed that by meeting the proposed standard that the number of premature deaths attributable to PM_{10} would also be halved.

On the basis of these assumptions it was estimated that approximately 600 premature deaths would avoided each year by meeting the proposed PM_{10} standard of 50µg/m^3 with associated savings to the health system of $4.3 billion (AAQ NEPM revised Impact Statement, p 127).

Available data indicated that the PM_{10} 50 μg/m^3, 1-day average was only occasionally exceeded in major airsheds in most years. Little emission inventory data were available on $PM_{2.5}$ and it was judged that a single PM_{10} standard would be complementary and most easily monitored at that time. The project team estimated that the PM_{10} standard would be the equivalent in some air sheds to a 20 to 30μg/m^3 standard for $PM_{2.5}$. Hence it was recommended that the standard for particles be for PM_{10} at 50μg/m^3 averaged over a 1-day period.

2.5 Form of the standards and their application

As previously discussed the standards in the AAQ NEPM do not apply to the control of individual point sources. They were developed to apply to air quality across a region or air shed and not in locations that are directly influenced by specific sources.

The standards contained in the NEPM are compliance standards. These standards establish a maximum concentration, with a goal (number of allowable exceedences) set based on the achievability of the standard over a specified time frame. The standards and allowable number of exceedences are to be met within 10 years of the making of the NEPM (i.e. by 2008).

Under the provisions of the NEPC Act 1994 the standards became legally binding on jurisdictions when the NEPM was made in 1998. Jurisdictions were required to establish monitoring networks to assess compliance with the standards and to take actions to improve air quality to ensure that the standards and associated goals were met by 2008.

Monitoring for assessing compliance with the standards is conducted at performance monitoring stations. These stations have been established in accordance with jurisdictional monitoring plans approved by NEPC.

2.6 Review of $PM_{2.5}$, sulfur dioxide and ozone

When the NEPM was made a set of future actions were agreed to by NEPC. These future actions arose from issues raised through the development of the NEPM. The future actions included:

- by 2001 commence a review of the particles standard, in particular, the need for a standard less than 2.5 microns
- by 2003 commence a review of the practicability of developing a 10 minute sulfur dioxide standard
- by 2003 commence a review of the practicability of setting a long-term goal (> 10 years) of achieving a one hour average standard for photochemical oxidants of 0.08ppm measured as ozone within major urban airsheds.

The outcomes of these future actions are summarised below. In addition NEPC established a Risk Assessment Taskforce (RATF) to evaluate the use of risk assessment in developing air quality standards in Australia. The RATF reported to NEPC in 2001 and made recommendations that a risk assessment approach be used in the development and review of air quality standards. The approach used would be pollutant specific and be dependent on the data available. The report of the RATF is available on the EPHC website www.ephc.gov.au.

2.6.1 $PM_{2.5}$ review

In 2001 NEPC commenced the review of the need for a standard for $PM_{2.5}$. At that time the most recent information on the health effects of $PM_{2.5}$ was reviewed. This review included information from studies conducted in Australia as well as international studies.

The review identified that there were adverse health effects associated with exposure to $PM_{2.5}$. The effects included increases in daily mortality, hospital admissions and emergency room attendances and exacerbation of asthma associated with daily changes in ambient particle levels. The results of some of studies conducted with $PM_{2.5}$ had indicated that this size fraction may be more important than total PM_{10} for explaining the health effects attributed to exposure to particles.

Populations that had been shown to be susceptible to the effects of $PM_{2.5}$ included the elderly; people with existing respiratory disease such as asthma, chronic obstructive pulmonary disease (COPD) and bronchitis; people with cardiovascular disease; people with infections such as pneumonia; and children. Results of epidemiological studies had provided no evidence for the existence of a threshold value below which no adverse health effects are observed.

Australian studies had also shown adverse health effects associated with exposure to $PM_{2.5}$ (EPA Victoria, 2001, 2000; Petroeschevsky *et al*., 2001; Simpson *et al*., 2000; Morgan *et al*., 1998a, 1998b; Simpson *et al*., 1997). All of these studies had used nephelometry data as a surrogate for $PM_{2.5}$.

Studies in Melbourne, Sydney and Brisbane have found that increases in daily mortality (all cause, respiratory and cardiovascular causes) are associated with increases in fine particles (bsp) (EPA Victoria 2000; Simpson *et al*., 2000; Morgan *et al*., 1998a; Simpson *et al*, 1997). The results of the Melbourne study show that the results were not independent of the other pollutants except during the warm months. The Sydney and Brisbane studies found strong associations across the whole year. The strongest effects in all studies were found in the elderly.

The studies investigating the effects of $PM_{2.5}$ on hospital admissions found strong associations in Melbourne, Sydney and Brisbane for admissions for respiratory and cardiovascular disease, asthma (especially in children <14 years) and COPD (EPA Victoria, 2001; Petroeschevsky *et al*., 2001; Morgan *et al*., 1998b). As with the studies on daily mortality, the strongest associations found in these studies were in the elderly and children.

On the basis of the review it was recommended that a $PM_{2.5}$ standard be included in the AAQ NEPM and a variation to the NEPM undertaken. The standards for $PM_{2.5}$ were developed through a full quantitative risk assessment process using air quality data from Melbourne, Sydney, Brisbane and Perth. The risk assessment process followed the process recommended by the NEPC Risk Assessment Taskforce (NEPC, RATF report, 2001). The risk assessment process utilised the USEPA methodology and provided a range of estimates for both long-term and short-term (24-hour) standards. The avoidable health outcomes and associated costs and benefits were assessed for the achievement of each of the potential standards.

On the basis of the assessment of costs and benefits and consideration of achievability within a realistic timeframe, both a 24-hr and annual average standard were proposed. The health effects assessed in the development of the standards included:

- short-term effects
    - daily mortality (all causes – non-traumatic)
    - daily mortality (respiratory disease)
    - daily mortality (cardiovascular disease)
    - daily hospital admissions (asthma)
    - daily hospital admissions (cardiovascular disease)
    - daily hospital admissions (COPD)

- long-term effects
    - mortality (all cause – non-traumatic)
    - mortality (lung cancer)
    - mortality (cardiopulmonary disease).

Exposure response relationships from international studies were used in the risk assessment, as there were not sufficient Australian epidemiological data at that time to use data specific to Australian cities. The risk assessment was conducted for all ages with the exception of hospital admissions for cardiovascular disease and COPD that focussed on people >65 years of age.

In developing the standard consideration was given to the form of the standard. Three forms of the standard were considered. The types of standards that were considered for the variation are:

- Standard with Compliance Goal and Specified Monitoring and Reporting Protocol
- Advisory Reporting Standard
- Reporting Against a Protective Health Value.

At the time of the variation there was limited monitoring data for $PM_{2.5}$ in Australian cities. This made an assessment of the achievability of meeting the standard (and associated costs) difficult to determine. A range of potential standards were evaluated through the risk assessment process and the number of health outcomes avoided (both mortality and hospital admissions for a range of conditions) were estimated. Due to the difficulty in obtaining agreed information on the approach to costing mortality no attempt was made to provide a estimate of the costs associated with the number of deaths avoided for each potential standard. For hospital admissions data on the costs of admissions for each health outcome was obtained from the Australian Institute of Health and Welfare (AIHW, 1986, 1999). It was estimated that if the proposed standards were met then $4.5 million per year would be avoided in hospital admissions for the health outcomes considered in the risk assessment process. In addition approximately 1200 premature deaths would be avoided (Impact Statement for $PM_{2.5}$ variation, p 28, NEPC (2002).

Based on the difficulty in assessing the achievability and costs associated with meeting the $PM_{2.5}$ standards by 2008 due to lack of existing monitoring data at that time, it was recommended that $PM_{2.5}$ standards be incorporated into the NEPM via two advisory reporting standards.

An advisory reporting standard has the same numerical value as a compliance standard but without an associated goal setting a timeframe for compliance. The monitoring protocol associated with an advisory reporting standard established a reference method and monitoring and reporting requirements, but provided jurisdictions flexibility in relation to the timing and extent of monitoring they conduct. Any data collected is assessed against the advisory reporting standard. It was envisaged that the adoption of advisory reporting standards would facilitate data collection to ensure that sufficient data are available for the setting of a $PM_{2.5}$ compliance standard during the current review of the AAQ NEPM. The advisory reporting standards for $PM_{2.5}$ incorporated into the AAQ NEPM through the variation process are:

- 25µg/m^3 24–hour average
- 8µg/m^3 annual average

2.6.2 Review of Sulfur Dioxide standard

In 2003 a review of the practicability of developing a 10-minute sulfur dioxide standard commenced. As part of the review, jurisdictions conducted an analysis of 10-minute average sulfur dioxide levels recorded at NEPM monitoring sites as well as at some industry sites. The data indicated that levels of sulfur dioxide are low except in the vicinity of major point sources where there are occasional high levels recorded.

Through the consultation process there was broad acceptance by stakeholders that the Ambient Air Quality NEPM standards dealt with general population exposure and did not deal with the control of individual point sources. It was also noted by stakeholders that, because the existing NEPM monitoring networks have been established to assess general population exposure and are not located close to point sources, they would be unlikely to pick up elevated 10-minute levels. Consequently, additional data processing costs associated with 10 minute monitoring would not be warranted. The outcomes of the review were:

- the original decision not to include a 10 minute standard for sulfur dioxide in the Ambient Air Quality NEPM remained valid
- analysis of sulfur dioxide monitoring data by jurisdictions indicates that 10 minute levels are only of concern at a limited number of locations, usually close to point sources. Short-term levels at monitoring sites without significant impacts from major point sources are typically well below international guidelines
- short-term exposure to high levels of sulfur dioxide has been linked with adverse health effects
- some communities in the vicinity of point sources have concerns about the current management of emissions of sulfur dioxide in some jurisdictions. There was broad agreement amongst the majority of stakeholders that the Ambient Air Quality NEPM is not the most effective instrument for managing those impacts
- the need for other means of ensuring the health of communities in the vicinity of point sources is protected should be considered in consultation with health agencies
- broad issues raised by some stakeholders about the scope of the Ambient Air Quality NEPM and whether or not it should be varied to include point source monitoring are more appropriately considered in the current review of the NEPM (considered in previous discussion paper).

Based on the outcomes of the review NEPC endorsed the review recommendations that a 10-minute SO_2 standard should not be incorporated into the AAQ NEPM. To assist jurisdictions in managing the impact of short-term peaks of SO_2 in communities affected by

emissions from industrial point sources, NEPC further endorsed the recommendation that further work be pursued as a partnership between EPHC and the health sector to develop a short-term guideline value that could be used by individual jurisdictions.

2.6.3 Preliminary work for the review of the ozone standard

In making the National Environment Protection (Ambient Air Quality) Measure (the NEPM) in 1998, the National Environment Protection Council (NEPC) adopted:

- a one-hour ozone standard of 0.10 parts per million (ppm) and
- a four-hour ozone standard of 0.08ppm.

In October 2003, NEPC agreed that the practicability of tightening the one-hour ozone standard should be considered as part of the review of the NEPM as a whole, but that some preliminary work would commence in advance. This work would focus on which averaging periods would be most appropriate for ozone standards for the protection of the health of the Australian population. A number of issues were considered in the preliminary work.

Since 1998 the body of data suggesting a link between exposure to ozone and increases in daily mortality and hospital admissions especially during the warmer months has increased. Health studies have shown that adverse health effects are associated with exposure to ozone for different averaging periods.

A number of overseas jurisdictions (the World Health Organisation, the European Union, United States and California) have adopted eight-hour ozone standards (sometimes in conjunction with a 1-hour standard) on the basis that eight-hour ozone exposures have been judged to pose a significant health risk in those jurisdictions.

The analysis of ozone episodes in the major Australian urban airsheds showed that ozone peaks were typically of short duration. For example, the duration of periods when the one-hour average concentration exceeded 0.06ppm was one hour in 30 to 50% of cases; 2 hours in 20 to 30% of cases; and 5 hours or longer in up to 20% of cases. Sydney experienced the episodes of longest duration (up to 9 hours), followed by Melbourne and Perth (up to 7 hours). The extended durations for ozone levels were uncommon in Melbourne and Perth but not in Sydney.

Ozone monitoring data and ozone trends indicate that achieving the current ozone standard is a major challenge for Sydney. Should a stricter standard and an 8-hour standard, consistent with international standards/guidelines, be adopted, achievability could also become an issue for some of the other major urban airsheds.

Current estimates of background ozone levels in Australia range between 0.02 and 0.04ppm. This is a significant issue in assessing jurisdictions' ability to meet tighter standards or an 8-hour standard consistent with international guidelines/standards. There is no agreed methodology for calculating background levels more accurately.

Through the consultative process there was general support for a one hour averaging period combined with a longer averaging period. It was considered that the health data supported a one hour and an eight hour standard.

There was also a general view that averaging periods should reflect Australian conditions. However, there were differing opinions on what the Australian monitoring data indicated about the averaging periods. It was noted that the length of ozone episodes in most Australian airsheds suggested that a one and four hour standard was more relevant to Australian exposure and would be more suitable. However, it was also noted that the longer ozone episodes experienced in Sydney were the exception to this. It was suggested that a combination of one, four and eight hour standards could be considered. It was noted that an eight hour standard would make comparison with ozone monitoring results from other countries easier.

The preliminary work found that a combination of a one, four and eight hour averaging period is appropriate for the NEPM ozone standards to protect the health of the Australian population. This addresses the health concerns that prolonged exposure to ozone is a significant health risk and the analysis of Australian monitoring data which indicates that episodes of elevated ozone rarely last more than 4 hours in the major urban airsheds; the exception to this being Sydney.

2.6.3.1 One hour

Short term exposure to ozone for one to three hours can result in immediate and reversible health effects such as acute inflammatory responses. These responses are most likely to occur in susceptible groups in the population such as asthmatics, people with existing respiratory conditions, the elderly and young children. The major Australian airsheds all experience one hour ozone peaks on occasions and this averaging period should be retained.

2.6.3.2 Four hour

People experience increased health effects from ozone over time and at lower concentrations. Four hours is typically as long as elevated ozone levels last in the majority of the major urban airsheds i.e. Melbourne, Perth, Adelaide and Brisbane. For these airsheds a combination of a one and four hour standard, set at appropriate levels, should protect populations against ozone levels of concern.

2.6.3.3 Eight hour

As noted above, people experience increased health effects from ozone with prolonged periods of exposure. Studies show that over six to eight hours people experience decreased lung capacity when exposed to relatively low levels of ozone. Unlike the other major airsheds, six to eight hour episodes are reasonable common in Sydney in the warmer months.

Longer exposures of six to eight hours affect, in particular, groups such as outdoor workers and children playing and exercising outdoors in summer. An eight hour standard, in addition to one and four hour standards (set at appropriate levels) would offer protection against prolonged ozone exposures, as well as against shorter term peaks of concern.

2.6.3.4 Implications for jurisdictions

Any change to reporting requirements under the NEPM would be undertaken after the full review of the NEPM. No additional resources would be required by jurisdictions to monitor or calculate eight hour averages. The implications in terms of achievability will depend on the level at which the standard is set. The final levels at which the standards are set need to be determined taking into account economic, social and environmental considerations

including an analysis of the costs and benefits associated with any proposed standards. This will be done through the review of the AAQ NEPM and any proposed variation to the NEPM that may be required.

2.6.3.5 Achievability

The preliminary work found that the ozone standards should be health based but that achievability was a critical aspect of setting compliance goals. In determining the final standards a range of values should be considered and a cost benefit analysis should be conducted to examine the implications for jurisdictions of meeting these values. The analysis should take account of non-anthropogenic background levels that are estimated to range from 0.02–0.04ppm.

2.6.3.6 Other issues

The review of recent studies of the health impacts of ozone and the findings on health outcomes and susceptible groups reported in the issues paper and the summary of submissions document should be incorporated in the review of the NEPM.

The standards should seek to protect all sensitive groups in the community, and where susceptible groups are not able to be wholly protected by the standards, this should be explained. Children with asthma are considered to be a particularly significant sensitive subgroup in relation to ozone. Other sensitive subgroups are people with existing conditions such as chronic respiratory conditions and cardiovascular disease; the elderly; and people who may have an inherent genetic susceptibility to ozone. Active individuals who spend long periods outdoors in summer such as outdoor workers, children and athletes are also susceptible because of their potential exposure.

On the basis of the analysis conducted during the preliminary work and the outcomes of consultation the following recommendations were made to NEPC which "resolved to endorse the recommendations of the Report on the Preliminary Work for the Review of the Ozone Standard for consideration in the review of the Ambient Air Quality NEPM, viz:

- the appropriate averaging periods for ozone standards in the National Environment Protection (Ambient Air Quality) Measure (the NEPM) are one, four and eight hours
- the level at which the standards are set be determined as part of the review and any subsequent variation of the NEPM. The decision should be informed by an assessment of the health risk and population exposure
- a cost benefit analysis be conducted as part of the review and any subsequent variation of the NEPM which evaluates a range of possible compliance goals (including a base case which is the equivalent of the current values) to assess the achievability of meeting the options presented.

As part of the review and any subsequent variation of the NEPM, consideration be given to making achievability issues more transparent in setting the ozone standard, for example by setting a health based level and taking account of achievability via the methods set out in the report."

2.7 Summary

The establishment of air quality standards in the AAQ NEPM was the first time that national standards for air quality had been set in Australia. They were considered to be the first step

in establishing a consistent approach to the management of air quality across Australia. As discussed in the previous sections the standards were based on the understanding of the health effects of the pollutants at the time of making the NEPM in 1998. The standards adopted were generally consistent with international standards/guidelines in place in 1998.

Although there was acceptance of the standards by stakeholders the process for developing the standards was not consistent for each pollutant. This has also been the case in the development of the advisory reporting standards for $PM_{2.5}$ and the monitoring investigation levels contained in the air toxics NEPM. The absence of an overall agreed methodology was reflected in considerable debate across the health and environment sectors and with other key stakeholders during each of the processes. The areas of debate have gone beyond the broad standard setting framework and involve technical issues such as margins of safety required in the standards to protect sensitive groups, the use of epidemiological and toxicological data in the hazard assessment and the approaches to dealing with non-threshold pollutants.

As discussed in Section 1.5, to overcome these issues, EPHC established the SSWG to develop a nationally agreed approach to setting air quality standards in Australia. The draft standard setting process establishes a weight of evidence approach to the hazard assessment and establishes clear guidelines on how this is to be undertaken. It builds on the document prepared by the NHMRC on the approach to hazard assessment in the setting of air quality standards in Australia (NHMRC, 2007).

The following sections of this discussion paper evaluate new information on understanding of the health effects of air pollution that has arisen since 1998. The evaluation set out in Section 3 of this paper applies the weight of evidence approach developed by the SSWG to assess this new information and provide an evidence base for recommendations for possible changes to the existing standards in the AAQ NEPM. Any changes to the standards would be undertaken through a separate process to vary the existing NEPM.

3. NEW EVIDENCE OF HEALTH EFFECTS OF CRITERIA AIR POLLUTANTS

3.1 Introduction

The AAQ NEPM was made in 1998 and set standards for carbon monoxide, nitrogen dioxide, sulphur dioxide, particles (as PM_{10}), ozone and lead. In 2003 the NEPM was varied to include advisory reporting standards for $PM_{2.5}$. The process for developing the standards is discussed in Section 2 of this discussion paper.

At the time of making the NEPM there were no studies conducted in Australia linking adverse health effects with exposure to air pollution. Consequently the standards were based on evidence from studies conducted overseas, particularly the US. Since that time a number of studies have been conducted in Australia that supports the findings of studies overseas. These studies provide evidence of adverse health effects attributable to air pollution in the Australian population at pollution levels currently experienced in Australian cities. The current air pollution levels are largely below the current air quality standards in the NEPM although exceedances of the particle and ozone standards are experienced at times.

In 2004 EPHC established a working group (Standard Setting Working Group, SSWG) to develop a national approach, jointly between the health and environment sectors, to setting air quality standards in Australia. The SSWG methodology establishes a weight of evidence approach to hazard assessment that builds on the outcomes of a workshop conducted by NHMRC in 2006 (NHMRC, 2006). The weight of evidence analysis considers evidence from all scientific fields on the health effects of air pollution including epidemiology, controlled human exposure and animal toxicological studies. Higher weighting is placed on studies involving humans.

The key policy-relevant questions which provide a framework for review of the scientific evidence are:

1. Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of air pollutants found in the ambient air in Australian cities?
2. What do recent studies focused on the near source environments tell us about health effects of air pollutants?
3. At what levels of exposure to air pollutants do health effects occur?
4. Has new information altered conclusions when the NEPM was made regarding the plausibility of adverse health effects caused by exposure to air pollutants?
5. To what extent have important uncertainties been identified and addressed?
6. What are the relationships between short- and long-term exposures to air pollutants and adverse health effects?

Similar questions have guided the recent USEPA Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (USEPA, 2008a) and the USEPA Integrated Science Assessment for Oxides of Sulfur (2008b).

This review applies the approach to hazard assessment recommended by the SSWG to assess new evidence for the health effects of air pollution since the AAQ NEPM standards were established in 1998. It will identify if there have been any changes in the understanding of the health effects of air pollution, including key health outcomes,

susceptible groups or exposure response functions, in Australia or overseas since 1998 that would support the need to review the current standards. The review builds on work done by Curtin University for the Commonwealth Department of Health and Ageing as part of the review of the AAQ NEPM (Curtin University, 2008). The analysis will inform NEPC consideration of whether there is sufficient evidence to support a variation to the NEPM.

This review document sets out (1) an outline of the approach used to evaluate the health evidence, (2) a framework for determining causality and (3) consideration of the precautionary principle during the decision making process as to whether a review of the standards is needed. This is followed by an evaluation for each pollutant of:

- epidemiologic studies of health effects from short- and long-term exposures
- controlled human exposure studies related to short-term exposures
- toxicological studies conducted in animals.

3.1.1 Approach to assessment

A consistent and transparent basis for evaluating the causal nature of air pollution-induced health effects is important. Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, animal toxicological, human clinical, and in vitro studies) have been formulated by a number of regulatory and science agencies, for example the International Agency for Research on Cancer (IARC, 2006), USEPA Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 2005), and Centre for Disease Control and Prevention (2004). These approaches are similar in nature and have proven effective in providing a uniform structure for determining causality.

3.1.1.1 Establishing causality

The most compelling evidence of a causal relationship between pollutant exposure and health effects comes from controlled human exposure studies. Controlled human exposure studies evaluate health effects linked to exposure under controlled laboratory conditions.

In epidemiologic or observational studies of humans, exposures reflect real world exposures to a pollutant mix. Observational studies can describe associations between exposure and effect through a variety of study designs including cross-sectional, case-control, cohort, time-series, and panel studies. Situations such as closure or elimination of a pollution source (Hedley et al, 2002) provide study opportunities to compare health effects before and after an exposure change. They can provide compelling evidence of causality.

Experimental animal data complement clinical and observational data. In the absence of clinical or epidemiologic data animal data may be used to support likely causal determination where humans are assumed or known to respond similarly to the animal studied.

Much of the available health information in this review comes from epidemiologic studies that report a statistical association between exposure and health outcome. Many of the health outcomes reported in these studies have complex etiologies and depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors.

Moving from association to causation involves eliminating alternative explanations for the association. An association is prima facie evidence for causation; alone, however, it is insufficient proof of a causal relationship between exposure and disease. "Cause" explains a significant relationship between exposure to an air pollutant and an associated health effect. "Association" is the statistical dependence among events, characteristics, or other variables.

A lack of observable effects from controlled human exposure studies does not necessarily mean that a causal relationship does not occur. One limitation is a small study population, which restricts the ability to discern statistically significant findings. These studies are also confined to limited exposure conditions that can be feasibly studied. In addition, the most susceptible individuals or groups may be explicitly excluded for practical and ethical reasons. Intervention studies, because of their experimental nature, can be particularly useful in characterizing causation.

Inferring causation from epidemiologic studies requires consideration of uncertainties, particularly potential confounders. There are several ways to reduce the uncertainty in observed associations through statistical analyses including multivariate regression models, case control studies and stratified analyses. Appropriate statistical adjustment for confounders requires identification and measurement of all reasonably expected confounders.

Confidence that measurement errors, including unmeasured confounders, are not biasing the results is increased when multiple studies are conducted in various settings using different populations or exposures. Thus, multicity studies which use a consistent method to analyse data from across locations with different levels of co-pollutants can provide insight on potential confounding in associations. Multivariate models are the most widely used strategy to address confounding in epidemiologic studies, but such models need to be carefully interpreted when assessing effects of air pollutants.

Estimating the causal influence of an exposure to an air pollutant on a health outcome is an uncertain one. There are two distinct levels of uncertainty that need to be considered:

1. Model uncertainty—uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences.
2. Parameter uncertainty—uncertainty as to the statistical estimates within each model.

Assessment of model uncertainty involves: (1) whether exposure causes the health outcome; (2) the set of confounders associated with exposure and health outcome; (3) which parametric forms best describe the relationships among exposure, confounders, and outcome; and (4) whether other forms of bias could be affecting the association.

In evaluating the scientific evidence on health effects of exposure to air pollutants there are two steps needed to address the policy-relevant questions noted above:

1. What are (if any) the effects of the air pollutant under consideration on susceptible populations, given the total body of evidence.
2. At what levels of exposure do health effects of concern occur.

The first step determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the exposure-response relationships and the levels, duration and pattern of exposures at which effects are observed.

Statistical methods cannot establish proof of a causal relationship but can define an association with a certain probability. The causal significance of an association is a matter of judgment that goes beyond any statement of statistical probability. To assess the causal significance of an air pollutant and a health effect, the USEPA state that a number of criteria must be used, no one of which is distinctly characteristic of a particular disease by itself (USEPA, 2004).

To aid judgment, various "aspects" of causality have been developed the most widely cited being those of Bradford Hill (1965). The Hill viewpoints were developed for use to assist in the interpretation of epidemiology data and have been modified by the USEPA for use in causal determinations specific to health and environmental effects and pollutant exposures. The USEPA modified the Bradford Hill viewpoints for use with a broader array of data, including epidemiologic, human clinical, and animal toxicological studies, as well as in vitro data. Table 3.1 sets out the USEPA aspects to aid in judging causality for air pollution effects and these have been applied in this review conducted as part of the AAQ NEPM review.

Table 3.1 Aspects to aid judging causality (Adapted from the USEPA, 2008).

1. Consistency of the observed association.	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
2. Strength of the observed association.	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, a pollutant of lower potency, or a common disease with a high background level.
3. Specificity of the observed association.	This refers to increased inference of causality if one cause is associated with a single effect or disease. The USEPA now consider this to be one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.
4. Temporal relationship of the observed association.	A causal interpretation is strengthened when exposure is known to precede development of the disease.
5. Biological gradient (exposure-response relationship).	A clear exposure-response relationship (e.g. increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g. increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biological gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.
6. Biological plausibility.	An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of biological understanding, however, is not a reason to reject causality.
7. Coherence.	An inference of causality may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. For instance, similar findings between clinical and animal studies, or closely related health effects, which are expected to be associated with exposure, are in fact observed together. The absence of other lines of evidence, however, is not a reason to reject causality.
8. Experimental evidence (from human populations).	Experimental evidence is generally available from human populations for the criteria pollutants. The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies (e.g., intervention studies).
9. Analogy.	Structure activity relationships and information on an agent's structural analogues can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogues, can inform decisions regarding likely causality.

While these aspects provide a framework for assessing the evidence, they do not lend themselves to consideration in terms of simple formulas or fixed rules of evidence leading causality conclusions (USEPA, 2008a, b). These considerations are taken into account with

the goal of producing an objective appraisal of the evidence. The principles in Table 3.1 cannot be used as a strict checklist, but rather as a determination of the weight of the evidence for inferring causality. In particular, the absence of one or more of the principles does not automatically exclude a study from consideration.

3.1.1.2 Evaluating weight of evidence

A weight of evidence evaluation is based on various lines of evidence from human clinical and epidemiologic studies as well as animal studies and in vitro studies. The separate judgments are then integrated into a qualitative statement about the overall weight of the evidence and causality. Further issues to be considered in evaluating the weight of evidence for an effect relate to characterizing exposure and risk to populations i.e. at what levels do health effects occur? To address these issues the following questions need to be considered:

1. What is the exposure-response relationship?
2. Under what exposure conditions (dose or exposure, duration and pattern) are effects seen?
3. What population groups appear to be affected or more susceptible to effects?

For the purpose of this review the hierarchy developed the USEPA (2008a) has been adapted to guide the weight of evidence evaluation for determination of causality (Table 3.2).

Table 3.2 Weight of evidence for causal determination (adapted from USEPA, 2008a)

Sufficient to infer a causal relationship	Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposure and the outcome. Causality is supported when an association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. That is, human clinical studies provide the strongest evidence for causality. Causality is also supported by findings from epidemiologic "natural experiments" or observational studies supported by other lines of evidence. Generally, determination is based on multiple studies from more than one research group.
Sufficient to infer a likely causal relationship (i.e. more likely than not).	Evidence is sufficient to conclude that there is a likely causal association between relevant pollutant exposures and the outcome. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, observational studies show associations but confounding and other issues are difficult to address and/or other lines of evidence (human clinical, animal, or mechanism of action information) are limited or inconsistent. Generally, determination is based on multiple studies from more than one research group.
Suggestive, but not sufficient to infer a causal relationship	Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but is weakened because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an association, while the results of other studies are inconsistent.
Inadequate to infer the presence or absence of a causal relationship	The available studies are inadequate to infer the presence or absence of a causal relationship. That is, studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. For example, studies which fail to control for confounding or which have inadequate exposure assessment, fall into this category.
Suggestive of no causal relationship	The available studies are suggestive of no causal relationship. That is, several adequate studies, examining relationships between relevant population exposures and outcomes, and considering sensitive subpopulations, are mutually consistent in not showing an association between exposure and the outcome at any level of exposures. In addition, the possibility of a small elevation in risk at the levels of exposure studied can never be excluded.

The main aim of setting NEPM standards is the prevention of adverse health impacts from air pollution and to provide adequate protection for all Australians. For the purpose of setting air quality standards, the risk characterisation applies to population risk not individual risk. Population risk refers to an assessment of the extent of harm for the population as a whole. In determining the risk of adverse health effects in the population from exposure to air pollution, evidence of causality is largely drawn from estimates of how the risk changes in response to exposure. Generally, the response is evaluated within the typical range of air pollutant concentrations experienced by a defined population. Extensive human data are available to inform risk assessments for all criteria pollutants.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the exposure-response relationship is linear across the full concentration range or whether there is a threshold for effect.

Another factor that must be taken into account when setting air quality standards is the existence of vulnerable subgroups within the population. The sensitivity of individuals to air pollution arises from a number of factors including:

- age, gender
- respiratory diseases, e.g., asthma, COPD
- cardiovascular diseases
- pre-existing disease, e.g. diabetes
- adverse birth outcomes: e.g. preterm birth, low birth weight, birth defects
- race/ethnicity
- genetic factors
- obesity
- socioeconomic status.

These factors may affect an individual's response to exposure to air pollution and air quality standards must contain an adequate margin of safety to protect these individuals as far as practicable.

3.1.2 The Standard Setting Working Group methodology

The SSWG methodology to assess the health effects of air pollutants, i.e. hazard assessment, applies a weight of evidence analysis to identify key health outcomes, vulnerable groups and exposure response functions for each of the pollutants. This analysis is guided by the application of the modified Bradford-Hill viewpoints for causality as set out in Table 3.1. Greater weighting is given to studies that been conducted on human populations but provides guidance on the use of animal data where human data is unavailable. The methodology also provides guidance on what constitutes an adverse health effect for the purpose of setting air quality standards.

International agencies such as the WHO, USEPA, EU, Californian EPA and DEFRA and UK Department of Health have all conducted extensive reviews of the health effects of air pollution in recent years. The approach taken in this review, as recommended by SSWG, has been to start with evaluation of the existing reviews undertaken by these agencies. The findings of these reviews are then expanded by an evaluation of any new literature that has been published since those reviews and an evaluation of studies conducted in Australia. The approach taken for this hazard assessment is summarised below:

Apply SSWG methodology for weight of evidence analysis

1. Evaluate findings of recent reviews from international agencies
2. Identify short-term and long-term effects from epidemiological studies
3. Identify outcomes of controlled human exposure and animal toxicological studies as supporting evidence for effect
4. Identify key health outcomes, susceptible groups and key studies used as basis for air quality standards by these agencies
5. Identify any new studies that have been published since latest reviews that add to the overall weight of evidence for effect
6. Review Australian air pollution and health studies and put in context with international data
7. Summarise weight of evidence for change of AAQ NEPM standards
8. Identify key health outcomes, susceptible groups and key studies that should be used as basis for review of air quality standards in the AAQ NEPM (if review is required)

9. Recommend whether Australian data is sufficient to be used as basis of change to standards or whether international data needs to be used.

This analysis will be conducted for each of the pollutants covered by the AAQ NEPM.

3.2 Carbon Monoxide

3.2.1 Introduction

In recent years the health effects of CO linked to ambient exposures have been well studied and reviewed by international agencies (USEPA, 2000, 2009; WHO, 2000; OEHHA, 2000). A comprehensive evaluation of the evidence relating to CO in ambient air and impacts on health is contained in *AAQ NEPM Health Reviews 2009 (www.ephc.gov.au)*.

Most of the recent studies have been population based epidemiological studies and have examined changes in mortality and morbidity, including hospital admissions and emergency room attendances. In addition there have been a number of studies investigating the association between ambient CO and adverse birth outcomes such as low birth weights and intrauterine growth retardation.

3.2.2 Mortality

Studies investigating the links between short-term changes in ambient CO have been examined in time-series studies of daily exacerbations of pre-existing cardiovascular and respiratory disease and mortality and have yielded mixed results. A number of multi-city studies have been conducted in recent years (Dominici *et al*., 2003; Burnett *et al*., 2004; Samoli *et al*, 2007). The results of these multi-city studies reported comparable CO mortality risk estimates for total (non-accidental) mortality. The APHEA2 European multi-city study (Samoli *et al*., 2007) showed slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when examining potential confounding by co-pollutants these studies consistently showed that CO mortality risk estimates were reduced when NO_2 was included in the model, but this observation may not be "confounding" in the usual sense in that NO_2 may also be an indicator of other pollutants or pollution sources (i.e., traffic) (USEPA, 2009).

The APHEA study (Samoli *et al*., 2007) performed a sensitivity analysis, which indicated an approximate 50–80% difference in CO risk estimates from a reasonable range of alternative models. In addition, the study examined the CO-mortality exposure-response relationship through a search of varying threshold points, and found only weak evidence of a CO threshold at 0.5 mg/m^3 (0.43ppm), but this result was complicated by the lowest 10% of the CO distribution for seven of the 19 cities examined being at or above 2 mg/m^3 (1.74ppm) (USEPA, 2009).

The results of several single city studies support the findings of the multi-city studies in that some evidence of a positive association was found for mortality upon short-term exposure to CO. Some studies conducted in the US, Canada and Europe have shown positive associations with mortality with cardiovascular mortality most strongly linked to exposure to CO (REFS). However, in many of the studies controlling for other pollutants reduced the effect estimate for CO and in some cases the association became non-significant (REFS). A study conducted in Melbourne found a significant positive association between 5-day average 8-hour concentration of CO and cardiovascular deaths (all ages). The effects

observed for CO were stronger in the warm season compared with the cool season, with significant associations found in the warm season for respiratory and all cause mortality (Denison *et al*., 2000).

The USEPA concluded that the evidence from the recent multi- and single-city studies suggests that an association between short-term exposure to CO and mortality exists, but limited evidence is available to evaluate cause-specific mortality outcomes associated with CO exposure. It is unclear if CO is acting alone or as an indicator for other combustion-related pollutants. In addition, the results underscore the limitation of current analytical methods to disentangle the health effects associated with one pollutant in the complex air pollution mixture. Overall, the epidemiologic evidence is suggestive of a causal relationship between short-term exposure to environmentally relevant CO concentrations and mortality (USEPA, 2009).

The most recent review of the health effects of CO conducted by WHO was 2000 as the basis of the air quality guidelines for Europe (WHO, 2000). CO was not reviewed for the global update conducted in 2005. The WHO acknowledged that there were new studies that indicated the significance of CO as a pollutant associated with the health effects. The WHO working group agreed that, while the evaluation of the newly accumulated epidemiological data might be warranted, CO should not be included in the 2005 update, also because of limited resources and time frame of the project.

3.2.3 Hospital admissions and emergency department attendances

Since the NEPM was made in 1998 there have been a number of studies that have found associations between hospital admissions and emergency department attendances and short-term exposure to CO. The associations were strongest for people with existing cardiovascular disease and the elderly (>65 years). Studies of hospital admissions and emergency department visits for ischemic heart disease (IHD) and congestive heart failure (CHF) provide the strongest evidence of ambient CO being associated with adverse cardiovascular outcomes.

Ballester *et al*. (2006) extended this research to include data from 14 Spanish cities for the period of 1995 to 1999. An average exposure period over lags 0-1 was analysed and for the combined estimates a 0.75ppm increase in 8-h max CO concentration was associated with a 1.77% (95% CI: 0.56–2.99) increase in all cardiovascular emergency hospital admissions and a larger increase of 3.57% (95% CI: 1.12–6.08) for heart disease admissions. These results persisted in two-pollutant models that included NO_2, O_3 and SO_2.

Barnett *et al*., 2006, examined associations between ambient CO concentrations and increased hospital admissions for various CVD outcomes. This study analysed data from 5 of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998–2001. A time-stratified case-crossover design was employed and the age groups of 15–64 years and ≥ 65 years were analysed for the 0–1 lag period. Results were combined across cities using a random-effects meta-analysis. Pollutants considered were nitrogen dioxide, carbon monoxide (8-hr CO range of means 5 Australian cities 0.80-1.7ppm), daily measures of particles (PM_{10} and $PM_{2.5}$) and ozone. Where multiple pollutant associations were found, a matched case-control analysis was used to identify the most consistent association. The pooled estimates across all cities showed that a 0.9ppm increase in 8–h max CO concentration was associated with a 2.3% (95% CI: 0.7–3.2) increase in admissions for ischemic heart disease (IHD) and a 2.9%

(95% CI: 0.6–4.1) increase in admissions for myocardial infarction (MI), but only among the elderly group (≥ 65 years). No association was found for admissions for stroke or arrhythmia in any age group. The combined estimates from the study also showed that an increase of 0.9ppm in the average 8-h max CO concentration over the current and previous day (lag 0-1) was associated with a 2.2% (95% CI: 0.9–3.8) increase in all CVD admissions, 2.8% (95% CI: 1.3–4.4) in all cardiac disease and 6% (95% CI: 3.5–8.5) in cardiac failure among those aged 65+ years. Among those aged 15–64 years there was a smaller increase in CVD admissions (1.0% [95% CI: 0.2–1.7]). In the elderly, all pollutants except O_3 were significantly associated with five categories of cardiovascular disease admissions. In matched analyses, CO had the most consistent association (Barnett *et al*., 2006).

Single city studies conducted in Australian cities have found consistent associations with hospital admissions and emergency department attendances for cardiovascular outcomes and CO (Jalaludin *et al*., 2007; Hinwood *et al*, 2006; Denison *et al*., 2001). The strongest effects are found in the elderly. Using a time-series approach, Jalaludin *et al*., (2007) examined the association between CO and emergency department attendances for single-day lags of 0, 1, 2, 3 and an average over lags 0 and 1 were. A 0.75ppm increase in 8-h max CO concentration for single-day lags 0 and 1 was associated with increases in attendances of 2.5% (95% CI: 1.6–3.5) and 1.4% (95% CI: 0.5–2.4) respectively. Based on an average over lags 0 and 1 (e.g., lag 0–1) there was an increase of 2.6% (95% CI: 1.5–3.6). There were positive increases of approximately 3% in CVD emergency department visits during the cool (May-October) period, but not the warm period (November-April). A 0.75ppm increase in 8-h max CO concentration (lag 0) was also associated with increases in IHD emergency department visits of 3.1% (95% CI: 1.3–4.9). No association was found between CO and stroke in the full year analysis. When the analyses were stratified by cool and warm periods a 0.75ppm increase in 8-h max CO concentration during the cool period was associated with a 3.8% (95% CI: 0.76–6.94) increase in stroke emergency department visits.

Strong significant positive associations were found between CO and hospital admissions in Melbourne (Denison *et al*., 2001). The strongest associations were found for admissions for cardiovascular disease in the elderly (65+ years) and all ages groups, admissions for ischemic heart disease and admissions for asthma in the 0–14 year age group. The results of the seasonal analysis revealed that the associations were strongest in the cool season, although significant positive associations were also observed for respiratory admissions (65+ years and all ages), asthma admissions (0–14 years) and cardiovascular admissions in the warm season. A 1ppm increase in 3-day average 8-hour CO was associated with a 3.29% and 2.72% increase in risk of admission for cardiovascular disease in the 65+ and all ages groups respectively. A 3.68% and 2.3% increase in admissions for ischemic heart disease was associated with a 1ppm increase in 1-hour maximum and 8-hour maximum CO respectively. The association between admissions for cardiovascular disease and ischemic heart disease and CO remained after controlling for other pollutants, however, the associations found with asthma and CO were removed after controlling for NO_2 and particles.

In Western Australia 263 children at high risk of developing asthma or atopy were recruited antenatally and all respiratory symptoms experienced by the children were recorded by their parents for five years and compared to ambient pollutant levels. Logistic regression models investigating relationships between individual air pollutants and respiratory symptoms showed significant associations between CO (8hr) and wheeze/rattle and runny/blocked nose (lag 5 and additive exposure over 5 days). Mean 8-hr CO was 1.4ppm throughout the study period (Rodriguez *et al*. 2007).

3.2.4 Birth outcomes

CO has been associated with birth and developmental outcomes in international studies. The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for preterm birth (PTB) and cardiac birth defects (USEPA, 2009). A number of studies have been conducted looking at varied outcomes, including PTB, birth defects, foetal growth (including LBW), and infant mortality.

There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. Studies to investigate the PTB outcome were conducted in California, and these reported consistent results whereby all studies reported a significant association with CO exposure during early pregnancy, and exposures were assigned from monitors within close proximity of the mother's residential address. Additional studies conducted outside of the U.S. provide supportive, though less consistent, evidence of an association between CO concentration and PTB (USEPA, 2009).

Very few epidemiologic studies have examined the effects of CO on birth defects (USEPA, 2009). Two of these studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. This insult to the heart is coherent with results of human clinical studies demonstrating the heart as a target for CO effects. Animal toxicological studies provide additional evidence for such an insult to the heart, and reported transient cardio-megaly at birth after continuous in-utero CO exposure (60, 125, 250 and 500ppm CO), delayed myocardial electro-physiological maturation (150ppm CO), or systemic splenic immuno-compromise (75 or 150ppm CO). Toxicological studies have also shown that exogenous continuous in utero CO exposure (250ppm) induced teratogenicity in rodent offspring in a dose-dependent manner that was further exacerbated by dietary protein restriction (65ppm CO) or zinc depletion (500ppm CO). Toxicological studies of exogenous CO exposure over the duration of gestation have shown skeletal alterations (7 h/day, CO 250ppm) or limb deformities (24 h/day, CO 180ppm) in prenatally exposed offspring.

There is evidence of ambient CO exposure during pregnancy having a negative effect on foetal growth in epidemiologic studies (USEPA, 2009). In general, the reviewed studies, reported small reductions in birth weight (ranging ~5–20g). Several studies examined various combinations of birth weight, LBW, and small for gestational age (SGA)/intrauterine growth restriction (IUGR) and inconsistent results are reported across these metrics. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population, or a marked effect in some subset of births.

Two studies in Australia have examined the association between birth outcomes and ambient CO. Mannes *et al*. (2005) estimated the average exposure during pregnancy to five common air pollutants for births in metropolitan Sydney between 1998 and 2000. The effects of pollutant exposure in the first, second, and third trimesters of pregnancy on risk of "small for gestational age" (SGA), and of pollutant exposure during pregnancy on birth weight were examined. Of the 138,056 singleton births; 9.7% of babies (13,402) were classified as SGA. In linear regression models carbon monoxide and nitrogen dioxide concentrations in the second and third trimesters had a statistically significant adverse effect on birth weight. For a 1ppm increase in mean carbon monoxide levels a reduction of 7 (95% CI, -5.0–19.0%) to 29 (95% CI, 7.0–51.0%) grams in birth weight was estimated.

Jalaludin *et al*. (2007) investigated the effect of prenatal exposure to six common urban air pollutants in the Sydney metropolitan area on pre-term birth between January 1, 1998 and December 31, 2000. Exposure to each air pollutant was estimated for the first trimester, the three months preceding birth, the first month after the estimated date of conception and the month prior to delivery and no clear impact of air pollutants on gestational age was found (Jalaludin *et al*., 2007).

3.2.5 Threshold for effect and sensitive groups

The results of epidemiological studies have found no evidence for a threshold below which adverse health effects in sensitive groups have not been observed after exposure to CO. The most sensitive groups to the effects of CO are people with existing cardiovascular disease, including ischemic heart disease and the elderly.

3.2.6 Findings of the review of the carbon monoxide health evidence

Australian studies have found associations between CO and cardiovascular hospital admissions and mortality, especially in the elderly for cardiac failure, myocardial infarction and ischemic heart disease with effects higher in the cool season. Associations have also been found with some birth outcomes such as low birth weights. The results of these studies are consistent with the findings of international studies. The most vulnerable groups for these effects are people aged 65 years and older as well as unborn foetuses.

Studies of hospital admissions and emergency department visits for ischemic heart disease (IHD) and congestive heart failure (CHF) provide the strongest evidence of ambient CO being associated with adverse CVD outcomes.

The USEPA found that it was difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if CO is a marker for the effects of another traffic related pollutant or mix of pollutants (USEPA, 2009). On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road locations. Although this complicates the efforts to disentangle specific CO-related health effects, the evidence indicates that CO associations generally remain robust in co-pollutant models, are coherent with the effects demonstrated by controlled human exposure and animal toxicological studies, and supports a direct effect of short-term CO exposure on cardiovascular morbidity at ambient concentrations below the current national ambient air quality standards (NAAQS) in the US. The USEPA concluded that such direct effects are plausible considering that long-term, low concentration CO exposure could result in a COHB level approaching those used in controlled human exposure studies.

3.2.6.1 Implications of the health evidence for the carbon monoxide NEPM standard

The USEPA concluded that short-term CO exposure impacts on cardiovascular morbidity at ambient concentrations below the current national ambient air quality standards (NAAQS) in the US. There is also clear evidence from Asutralian studies of health effects below the current Australian standards in the AAQ NEPM. These observations are also supported by the WHO.

3.3 Nitrogen Dioxide (NO_2)

3.3.1 Introduction

In recent years the health effects of NO_2 linked to ambient exposures have been well studied and reviewed by international agencies (USEPA, 2008a; WHO, 2006; California EPA). A comprehensive evaluation of the evidence relating to NO_2 in ambient air and impacts on health is contained in AAQ NEPM 2009 Health Reviews.

The critical health outcomes identified in overseas and Australian epidemiology studies resulting from short term exposure to NO_2 are increased respiratory disease and symptoms, especially in asthmatic children, and changes in lung function. The evidence for the effects of long-term exposure to NO_2 is limited, but epidemiological studies of chronic exposures to NO_2 from indoor sources suggested increased risk of lower respiratory illness in children. There is also evidence to suggest an association between chronic NO_2 exposure and changes to growth in lung function.

There can be a high correlation between nitrogen dioxide levels and airborne particles, both are generated from the same combustion sources, and nitrogen dioxide is converted to nitrates and contributes to fine particle mass. Thus it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies (WHO, 2006).

3.3.2 Short-term exposure

3.3.2.1 Mortality

Results from several large U.S. and European multi-city studies and a meta-analysis study indicate positive associations between ambient NO_2 concentrations and the risk of all-cause (non-accidental) mortality (e.g. APHEA1 and 2; US National Morbidity, Mortality, and Air Pollution Study—NMMAPS). Effect estimates in these studies range from 0.5 to 3.6% excess risk in mortality per standardized increment (20ppb for 24-h averaging time, 30ppb for 1-h averaging time). In general, the NO_2 effect estimates were robust to adjustment for co-pollutants.

Australian multicity studies conducted since the last NEPM review in 1998 have found either similar or greater associations between ambient levels of NO_2 and increases in mortality than those reported in European studies (i.e. APHEA1 and 2). Australian studies report increases in mortality from between 0.11% and 0.9% for every 1ppb increase in NO_2 (Simpson *et al*. 2005a,b; Simpson *et al*. 1997; Hinwood *et al*. 2004; Denison *et al*. 2000). In the US NMMAP study, NO_2 showed statistically significant relative increases in daily mortality from 0.3% to about 0.4% per 10ppb (previous day concentration, lag 1). This effect remained but lost statistical significance after adjusting for PM_{10} and ozone.

Both cardiovascular and respiratory mortality have been associated with increased NO_2 concentrations in epidemiological studies, however, similar associations are observed for other pollutants, including particles and SO_2. The range of risk estimates for excess mortality is generally smaller for NO_2 than for other pollutants (USEPA, 2008a). In addition, while NO_2 exposure, alone or in conjunction with other pollutants, may contribute to increased mortality, evaluation of the specificity of this effect is difficult. Clinical studies that show haematologic effects and animal toxicological studies that show biochemical, lung host

defense, permeability, and inflammation changes provide limited evidence of plausible pathways by which risks of mortality may be increased with short-term exposures to NO_2, but the USEPA concluded that no coherent picture is evident at this time (USEPA, 2008a).

3.3.2.2 Respiratory effects, asthma and changes in lung function

A number of epidemiological, controlled human exposure, and animal toxicological studies have investigated the effect of NO_2 exposure on respiratory symptoms and lung function. International reviews of these studies concluded that they provide sufficient evidence to infer a relationship between short-term NO_2 exposures and an array of adverse respiratory health effects. The strongest evidence comes from controlled human exposure studies and epidemiological studies that control for the effects of co-occurring pollutants (US EPA 2008a; WHO, 2006).

A consistent association has been found in epidemiological studies between air pollution and hospital admissions, emergency department visits and visits to the doctor for respiratory symptoms and asthma in children. Evidence from time-series epidemiological studies indicate increased asthma symptoms and medication use as well as emergency room visits and hospitalization for asthma, particularly in children, at ambient NO_2 concentrations ranging from from 0.018 to 0.036ppm (24-hour average) (Anderson *et al* 1997, Atkinson *et al*. 1999, Galan *et al*. 2003, Hajat *et al*. 1999, Lee *et al*. 2006, Peel *et al*. 2005, Simpson *et al*. 2005a, Sunyer *et al*. 1997).

Australian studies have reported similar associations between hospitalization for respiratory effects, including asthma, and daily NO_2 as overseas studies (Morgan *et al*. 1998a; Barnett *et al*. 2005; Erbas *et al*., 2005; Jalaludin *et al*. 2004; Rodriguez *et al*., 2007), although the effect estimates have been mixed, and a few studies reported no associations (e.g. Petroeschevsky *et al*. 2001). In a meta-analysis of results from 5 Australian and 2 New Zealand cities Barnett *et al*. (2005) analysed hospital admissions for 3 age groups of children. Significant increases in hospital admissions for respiratory disease (1–4, 5–14 years) and asthma (5–14 years) were associated with interquartile range increases in either 1-hr or 24-hr NO_2. The largest association reported was a 6.0% increase in asthma admissions with a 5.1ppb increase in 24-hr NO_2 and the effect was not reduced by inclusion of PM_{10} in the analysis. The effect was not reduced by inclusion of PM_{10} in the analysis.

Clinical studies indicate that individuals with asthma are more susceptible to the effects of NO_2 compared with healthy individuals. However, the dose-response concentrations have not been adequately studied. In general young healthy subjects exposed to NO_2 at concentrations below 4ppm for several hours do not experience symptoms, changes in pulmonary function or increased airway resistance. However, exposures to NO_2 in the range of 1.5–2.0ppm can cause small, statistically significant effects on airway responsiveness in healthy individuals. In studies with asthmatics, short term exposure to NO_2 has been associated with increased airway reactivity following exposures to 0.2 to 0.3ppm NO_2 for 30 minutes to 2 hours, and enhanced inflammatory response after exposures to 0.26ppm NO_2 from 15 minute to 30 minutes, followed by an exposure to an airborne allergen (ARB and OHHEA, 2007a).

Animal toxicology data support the notion that nitrogen dioxide can induce toxic airway effects, including reduced host defence against microbiological agents and enhanced bronchial hyperresponsiveness in asthmatics to allergen and irritant stimuli. However, these effects have been described in experimental studies following exposure to nitrogen dioxide

concentrations far beyond current air quality guidelines and standards. There were no new studies identified that address these issues at concentrations that are considered to be environmentally relevant and that separate the effects of nitrogen dioxide from those of other pollutants (WHO, 2006).

3.3.2.3 Cardiovascular effects

International reviews generally agreed that the available evidence on cardiovascular health effects following short-term exposure to NO_2 is inadequate to infer the presence or absence of a causal relationship at this time (USEPA, 2008a; WHO 2006). Evidence from epidemiological studies of heart rate variability, repolarization changes, and cardiac rhythm disorders among heart patients with ischemic cardiac disease are inconsistent. In most studies, associations with particles were found to be similar or stronger than associations with NO_2.

A meta-analysis of the associations between pollutants and cardiovascular hospital admissions in the elderly in Brisbane, Canberra, Melbourne, Perth, Sydney, Auckland and Christchurch found significant associations between CO, NO_2, and particles and five categories of cardiovascular disease admissions. The two largest statistically significant increases were for cardiac failure, with a 6.9% increase for a 5.1-ppb unit increase in NO_2 and a 6.0% increase for a 0.9-ppm increase in CO (Barnett *et al*, 2006).

Studies of hospital admission and emergency department visits for cardiovascular diseases seem to indicate a nitrogen dioxide effect; however, separating the effects of other traffic-related pollutants is difficult. Positive associations have been reported in single-pollutant models between ambient NO_2 concentrations and hospital admissions or emergency department visits; however, most of the effect estimates were diminished in multi-pollutant models that also contained CO and particles. Mechanistic evidence of a role for NO_2 in the development of cardiovascular diseases from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis is also lacking. Furthermore, the effects of NO_2 on various haematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of NO_2 on the cardiovascular system (USEPA, 2008a).

3.3.3 Long-term exposure

3.3.3.1 Mortality

Results of cohort studies in the United States and Europe examining the relationship between long-term exposure to NO_2 and mortality have been inconsistent. Further, when associations were suggested, they were not specific to NO_2 but also implicated particles and other traffic indicators.

3.3.3.2 Respiratory morbidity and asthma incidence

International reviews varied slightly in their conclusions about the evidence for an association between long-term exposure to NO_2 and respiratory symptoms, and increases in asthma prevalence and incidence. The US EPA concluded that the epidemiological and experimental evidence is suggestive but not sufficient to infer a causal relationship between long-term NO_2 exposure and respiratory morbidity or asthma incidence (US EPA, 2008a). The California EPA (ARB and OEHHA, 2007b) concluded that the respiratory health effects of long-term exposure to NO_2 have been clearly demonstrated in several large-scale European studies (Ackermann-Liebrich *et al*. 1997, Schindler *et al*. 1998; Kramer *et al*. 2000;

Janssen *et al*. 2003), in a cross-sectional study of children in Alameda, California (Kim *et al*. 2004) and in the Children's Health Study in Southern California (Gauderman *et al*. 2004; Gauderman *et al*. 2005). All agreed that the high correlation among traffic-related pollutants makes it difficult to accurately estimate independent effects in the long-term exposure studies.

The WHO (2000, 2006) reported qualitative evidence from epidemiological studies of long-term chronic ambient exposures being associated with increased respiratory symptoms and lung function decreases in children at annual average concentrations of 50–75 µg/m^3 (0.026–0.040ppm or higher), which are consistent with findings from indoor studies; although they do not provide clear exposure–response information for NO_2. As with short-term studies, isolating the effects of NO_2 from other pollutants is difficult without the supporting evidence of appropriate clinical and toxicological studies, and the weight of evidence is less for long-term effects. Evidence from animal toxicological studies show that prolonged exposures can cause decreases in lung host defenses and changes in lung structure.

All international agency reviews agreed that studies of lung function, such as the Children's Health Study in California (Gauderman *et al*. 2004; Gauderman *et al*. 2005), demonstrate some of the strongest effects of long-term exposure to NO_2. California EPA noted in its review that the findings from the Children's Health Study of reduced lung growth in children exposed to higher levels of NO_2 over an eight-year period is especially important, since it is a risk factor for chronic diseases and premature mortality later in life (ARB and OEHHA, 2007b). These respiratory health effects have been observed in areas with average NO_2 level of 18 to 57ppb, with many in the range of 23 to 37ppb.

3.3.3.3 Cardiovascular effects

The available epidemiologic and toxicological evidence supporting that long-term exposure to NO_2 has cardiovascular effects is mixed. The Harvard Six City study (Dockery *et al*. 1993; Krewski *et al*. 2000) provides some evidence from the US of an association between long-term NO_2 concentrations and both all-cause and cardiopulmonary mortality. The investigators did not fit multi-pollutant models to these data, and NO_2 was highly correlated with other pollutants. The American Cancer Society (ACS) study (Pope, III *et al*, 2002) failed to find any effect of long-term exposure to NO_2 on cardiopulmonary mortality, while data from Europe (Nafstad *et al*. 2004), suggested an increased risk of all-cause mortality. Likewise, European studies provided some evidence of an effect of long-term exposure on lung cancer (Nyberg *et al*. 2000; Nafstad *et al*. 2004).

Some studies have found associations between chronic NO_2 exposure and cardiovascular disease. Wellenius (2005), Metzger *et al*. (2004), and Simpson *et al*. (2005b) all reported an effect of NO_2 on either hospital admissions or emergency room visits for cardiovascular disease after PM was taken into account. Peters *et al*. (2000) found a strong independent effect of NO_2 on increased risk of defibrillator discharges in patients with implanted defibrillators, while Rich *et al*. (2005) found that the effect of NO_2 on ventricular arrhythmia was null when $PM_{2.5}$ was included in the model. Pekkanen *et al*. (2002) found significant associations between risk of ST segment depression and ambient lag 2 day NO_2 in 45 adults with coronary artery disease. NO_2 was moderately correlated with the co-located particle measurements. Two pollutant models for particles and gases were not tested.

3.3.3.4 *Cancer*

The international reviews concluded that epidemiological studies conducted in Europe have shown an association between long-term NO_2 exposure and increased incidence of cancer, however, the animal toxicological studies have provided no clear evidence that NO_2 acts as a carcinogen (USEPA, 2008a). Both US EPA and WHO suggest that NO_2 may be acting as an indicator of traffic-related carcinogens, and thus the observed increased cancer incidence may be related to exposure of these carcinogens, such as PAHs (USEPA, 2008a; WHO, 2006).

3.3.3.5 *Reproductive and development effects*

The epidemiologic evidence does not consistently report associations between NO_2 exposure during pregnancy and intrauterine growth retardation; however, some evidence is accumulating for effects on preterm delivery and foetal effects (USEPA, 2008a; WHO, 2006). However, it is unclear whether there is an independent effect for nitrogen dioxide (WHO, 2006). Scant animal evidence supports a weak association between NO_2 exposure and adverse birth outcomes, but it provides little mechanistic information or biological plausibility for an association between long-term NO_2 exposure and reproductive or developmental effects (USEPA, 2008a).

In a review of Australian studies of birth outcomes, few significant associations were demonstrated with NO_2 (Sram *et al*. 2005). Associations were reported in a Sydney study of approximately 13 400 births of "small for gestational age babies", where NO_2 was the pollutant associated with the largest reduction in birth weight (34 grams per 0.001ppm nitrogen dioxide over the third trimester) (Mannes *et al*. 2005). Similar to the other epidemiological studies, this adverse effect may be due to a mixture of combustion pollutants rather than NO_2 per se. Two other studies in Brisbane reported no association between NO_2 and pre-term birth or sub-optimal foetal growth (Hansen *et al*. 2006, 2007).

3.3.4 *Susceptible groups*

Overseas agencies and Australian studies identified infants, children and the elderly (i.e., >65 years of age) as groups that are potentially more susceptible than the general population to the health effects associated with ambient NO_2 concentrations. Individuals with asthma and other chronic lung diseases and cardiovascular diseases are particularly vulnerable (USEPA, 2008a; ARB and OEHHA, 2007b). The WHO suggest that people with ischemic heart disease and accompanying congestive heart failure and/or arrhythmia constitute a subgroup particularly sensitive to the effects of ambient air pollutants associated with internal combustion engines, including NO_2 (WHO, 2006).

3.3.5 *Findings of the review of the nitrogen dioxide health evidence*

The effect estimates for NO_2 are robust even after adjusting for the confounding effects of other pollutants. Animal toxicological studies and human clinical trials provide supporting evidence for a mechanism for respiratory effects, with human studies showing cell damage in human lung cells exposed to NO_2 and increased airway reactivity in asthmatics.

The results from several large U.S. and European multi-city studies and a meta-analysis study observed positive associations between short-term ambient NO_2 concentrations and risk of all-cause (non-accidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in mortality per standardized increment. Australian studies have reported increases in mortality between 0.11% and 0.9% for every 1ppb increase in NO_2.

Because of the high correlation among traffic-related pollutants, it is difficult to accurately estimate independent effects in the long-term NO_2 exposure studies. However, more evidence has emerged since the last NEPM review linking long-term exposure and health effects. There is epidemiological evidence that exposure to annual average concentrations of between 0.03 and 0.04ppm NO_2 may lead to changes in lung growth in children, symptoms in asthmatic children, and preterm births.

3.3.5.1 Implications of the health evidence for the nitrogen dioxide NEPM standard

Overall, there is a large body of epidemiological evidence from overseas and Australian studies showing consistent and statistically-significant associations between adverse health effects and short-term exposure to NO_2 at levels below the current ambient air quality NEPM standards of 0.12ppm (1-hour average). Ambient NO_2 concentrations from 0.018 to 0.036ppm (24-hour average) have been associated with increased hospital admissions and emergency department attendance for respiratory symptoms, particularly in asthmatics and children.

3.4 Ozone

3.4.1 Introduction

In 2005 NEPC completed preliminary work for the review of the ozone standards (NEPC, 2005). This work focussed on what would be the appropriate averaging times for ozone standards in Australia based on health effects observed in epidemiological and controlled exposure studies as well as exposure patterns in Australian cities. The outcome of this work was a recommendation that the ozone standards in the NEPM should be based on 1, 4 and 8 hours averaging periods.

In recent years the health effects of ozone linked to ambient exposures have been well studied and reviewed by international agencies (USEPA, 2006; WHO, 2006; Cal EPA, 2005). A comprehensive evaluation of the evidence relating to ozone in ambient air and impacts on health is contained in *AAQ NEPM Health Reviews 2009*.

Most of the recent studies have been population based epidemiological studies and have examined changes in mortality and morbidity, including hospital admissions and emergency room attendances. In addition there have been a number of controlled human exposure studies investigating the association between ozone and respiratory symptoms and reduction in lung growth.

The health effects of ozone are related to different averaging periods. In this document the following terminology has been used to identify the different exposures and related health effects:

- Short-term—1–4 hour exposures
- Prolonged—6–8 hour exposures
- Long-term—months to year long exposures or multiple year exposures.

3.4.2 Short-term effects

The health effects that have been associated with short-term exposure (1-4 hours) to ozone include:

- increases in mortality, mainly from respiratory causes
- increases in hospital admissions and emergency department visits for respiratory disease, including asthma
- decreases in lung function
- increases in respiratory symptoms
- pain on inspiration
- bronchoconstriction,
- increased airway responsiveness,
- airway inflammation,
- epithelial injury,
- immune system activation, and
- host defence impairment

3.4.2.1 Mortality

In recent years a large number of studies have investigated the association between exposure to ozone and increases in mortality. Key findings have come from a number of multi-city time-series studies conducted worldwide, including Australia, which reported associations between O_3 and mortality. These studies include analyses using data from 90 U.S. cities in the National Mortality, Morbidity and Air Pollution (NMMAPS) study (Dominici *et al*., 2003) and from 95 U.S. communities in an extension to the NMMAPS analyses (Bell *et al*., 2004). The analyses conducted by Huang *et al*. (2005) used a subset of 19 U.S. cities and focused primarily on cause-specific mortality associations during the warm season. An additional study (Schwartz, 2005) used case-crossover design and data from 14 U.S. cities to further investigate the influence of adjustment for weather variables in the O3-mortality relationship. Results were also available from a European study, Air Pollution and Health: a European Approach (APHEA), using data from 23 cities (Gryparis *et al*., 2004) and 4 cities (Toulomi *et al*., 1997). The study by Simpson *et al*., (2004) investigated the association between ozone and mortality in Brisbane, Melbourne, Perth and Sydney.

The results of key studies relating ozone to mortality show significant associations for different causes, mainly respiratory and (to a lesser extent) cardiovascular (USEPA, 2006; WHO, 2006). The effects of ozone on mortality were detected mostly in the elderly, and the studies focusing on mortality in children are more variable.

The original 90-city NMMAPS analysis, with data from 1987 to 1994 found a significant association between mortality and 24-hr average O_3 concentrations during the warm season, but the association was not significant in analyses for the full year (Samet *et al*., 2000). The extended NMMAPS analysis included data from 95 U.S. cities and included an additional 6 years of data, from 1987-2000 (Bell *et al*., 2004), and significant associations were reported between O_3 and mortality. The effect estimate for increased mortality was 0.5% per 24-hr average O_3 measured on the same day (20ppb change; 95% CI: 0.24, 0.78), and 1.04% per 24-hr average O_3 in a 7-day distributed lag model (20ppb change; 95% CI: 0.54, 1.55). In analyses using only data from the warm season, the results were not significantly different from the full-year results; the effect estimate for increased mortality was 0.44% per 24-hr average O_3 measured on the same day (20ppb change; 95% CI: 0.14, 0.74), and 0.78% per 24-hr average O3 in a 7-day distributed lag model (20ppb change; 95% CI: 0.26, 1.30). The O_3-mortality associations were robust to adjustment for particles (USEPA, 2006).

Using a subset of the NMMAPS data set, Huang *et al*. (2005) focused on associations between cardiopulmonary mortality and O_3 exposure (24-hr average) during the summer

season only. The authors report a 1.47% increase per 20ppb change in O_3 concentration measured on the same day (95% CI: 0.54, 2.39) and a 2.52% increase per 20ppb change in O_3 concentration using a 7-day distributed lag model (95% CI: 0.94, 4.10) (USEPA, 2006). These findings suggest that the effect of O_3 on mortality is immediate but also persists for several days.

Using a case-crossover study design, Schwartz (2005) assessed associations between daily maximum concentrations and mortality, matching case and control periods by temperature, and using data only from the warm season. Confounding by weather, especially temperature, is complicated by the fact that higher temperatures are associated with the increased photochemical activities that are important for O_3 formation (USEPA, 2006). The reported effect estimate of 0.92% change in mortality per 40ppb O_3 (1-hr max, 95% CI: 0.06, 1.80) was similar to time-series analysis results with adjustment for temperature (0.76% per 40ppb O_3, 95% CI, 0.13, 1.40), suggesting that associations between O_3 and mortality were robust to the different adjustment methods for temperature.

The APHEA study, a European multi-city study, reported statistically significant associations between daily maximum O_3 concentrations and mortality, with an effect estimate of a 4.5% increase in mortality per 40ppb O_3 (95% CI: 1.6, 7.7) in four cities (Toulomi *et al*., 1997). In an extended analysis using data from 23 cities throughout Europe (Gryparis *et al*., 2004) a positive but not statistically significant association was found between mortality and 1-hr daily maximum O_3 in a full year analysis. Gryparis *et al*. (2004) noted that there was a considerable seasonal difference in the O_3 effect on mortality. Focusing on analyses using summer measurements, statistically significant associations with total mortality were found [1.8% increase per 30ppb 8-hr O_3 (95% CI: 0.8, 2.9)], cardiovascular mortality [2.7% increase per 30ppb 8-hr O_3 (95% CI: 1.2, 4.3)] and with respiratory mortality (6.8% increase per 30ppb 8-hr O_3, 95% CI: 4.5, 9.2).

Two multi-city mortality studies (Bell *et al*., 2004; Gryparis *et al*., 2004) have also reported associations for multiple averaging times. Bell and colleagues (2004) reported associations between mortality and 1-hr daily max, 8-hr daily max and 24-hr average O_3 concentrations. Effect estimates for associations with 1-hr O_3 were slightly larger than that reported for 8-hr O_3 concentrations, and both were slightly larger than the association with 24-hr average O_3, but the effect estimates did not differ statistically. The APHEA study (Gryparis *et al*., 2004) also reported effect estimates that were slightly larger with 1-hr than with 8-hr O_3 concentrations, but not significantly so.

Several meta-analyses have been conducted on the relationship between O_3 and mortality. These analyses reported fairly consistent and positive combined effect estimates ranging from 1.5 to 2.5% increase in mortality for a standardised change in O_3 (USEPA, 2006). Three meta-analyses evaluated potential sources of heterogeneity in O_3-mortality associations (Bell *et al*., 2005; Ito *et al*., 2005; Levy *et al*., 2005). The USEPA noted common findings across all three analyses, in that all reported that effect estimates were larger in warm season analyses, reanalysis of results using default GAM criteria did not change the effect estimates, and there was no strong evidence of confounding by particle (USEPA, 2006). Bell *et al*. (2005) and Ito *et al*. (2005) both provided suggestive evidence of publication bias, but O_3-mortality associations remained after accounting for that potential bias. The USEPA (2006) concluded that the "positive O_3 effects estimates, along with the sensitivity analyses in these three meta-analyses, provide evidence of a robust association between ambient O_3 and mortality."

A multi-city study by Bell *et al*., (2006) examined the shape of the exposure-response function for the O_3-mortality relationship in 98 U.S. urban communities for the period 1987 to 2000 specifically to evaluate whether a "safe" threshold level exists. Results from various analytic methods all indicated that any threshold would exist at very low concentrations, far below international O_3 standards, and nearing background levels (USEPA, 2006). In a subset analysis using only days that were below the level of the current US O_3 standards, the O_3-mortality association remained statistically significant with only a small change in the size of the effect estimate (USEPA, 2006). Further, in a subset analysis based on 24-hr average O_3 concentrations, the effect estimates decreased and lost statistical significance only when the maximum daily average concentration included was < 10ppb (Bell *et al*., 2006), which corresponds to daily maximum 8-hr average concentrations in U.S. cities that are within the range of background concentrations.

3.4.2.2 Morbidity

Short-term exposures to O_3 have been reported to induce a wide variety of respiratory health effects. These effects include a range of effects, such as morphological changes in the respiratory tract, pulmonary function decrements, respiratory symptoms, respiratory inflammation, increased airway responsiveness, changes in host defence capability, acute morphological effects, increased emergency department visits and hospital admissions, and effects on exercise performance. Short-term O_3 exposure has also been associated with increases in restricted activity days and school absences but evidence is limited for these effects (USEPA, 2007).

In the past decade, a number of studies have examined associations between O3 exposures and emergency department visits for respiratory causes (USEPA, 2006). Respiratory causes for emergency department visits include asthma, bronchitis, emphysema, pneumonia, and other upper and lower respiratory infections, such as influenza, but asthma visits typically dominated the daily incidence counts (USEPA, 2007). Significant positive associations between O3 and emergency department attendances for respiratory causes have been found in several studies - total respiratory (Delfino *et al*., 1997b, 1998b; Hernandez-Garduno *et al*., 1997; Ilabaca *et al*., 1999; Lin *et al*., 1999), asthma (Friedman *et al*., 2001; Jaffe *et al*., 2003; Stieb *et al*., 1996; Tenias *et al*., 1998; Tobias *et al*., 1999 ; Tolbert *et al*., 2000 ; Weisel *et al*., 2002), and COPD (Tenias *et al*., 2002). The effect estimates for associations between emergency department visits for asthma and short-term O_3 exposures from summer only analyses tended to be positive and larger compared to results from cool season or all year analyses (USEPA, 2006). The USEPA (2006) concluded that stratified analyses by season generally supported a positive association between O_3 concentrations and emergency department visits for asthma in the warm season.

A study examining emergency department visits for total and cause-specific respiratory diseases in Atlanta, GA over an 8-year period (Peel *et al*., 2005) found that ozone concentrations were associated with emergency department visits for total respiratory diseases and upper respiratory infections in all ages. A marginally significant association was observed with asthma visits (2.6% [95% CI: 0.5, 5.9] increase per 30ppb increase in 8-h max O_3), which became stronger when the analysis was restricted to the warm months (3.1% [95% CI: 0.2, 6.2] increase). In multi-pollutant models adjusting for PM_{10}, NO_2 and CO, O_3 was the only pollutant that remained significantly associated with upper respiratory infections. Another large asthma emergency department study was carried out during the months of May through September from 1984 to 1992 in St. John, New Brunswick, Canada (Stieb *et al*., 1996). The mean 1-h max O_3 level was 41.6ppb (range 0–160). Effects were

examined separately among children aged less than 15 years and in persons aged 15 years and older. A significant effect of O_3 on emergency department visits was reported among persons 15 years and older. There was suggestion of a threshold somewhere in the range below a 1-h max O_3 of 75ppb (USEPA, 2006).

Several studies carried out in one or two cities over a span of five or more years provide substantial additional evidence regarding O_3 effects on respiratory hospital admissions (Anderson *et al*., 1998; Burnett *et al*., 1999, 2001; Moolgavkar *et al*., 1997; Petroeschevsky *et al*., 2001; Ponce de Leon *et al*., 1996; Sheppard *et al*., 1999 [reanalysis Sheppard, 2003]; Yang *et al*., 2003). Moolgavkar and colleagues (1997) reported significant and robust O_3 effects on respiratory hospital admissions in adults 65 years and older in Minneapolis and St. Paul, Minnesota (mean 24-h average O_3 of 26.2ppb), but not in Birmingham, Alabama (mean 24-h average O_3 of 25.1ppb). The absence of effects in the southern city may reflect less penetration of O_3 into the indoor environment due to greater use of air conditioning, and thus less correlation between central site O_3 monitoring and actual exposures of the general popualtion (USEPA, 2006).

Ozone effects on all-age and age-stratified asthma and total respiratory hospital admissions were observed in Brisbane, Australia (Petroeschevsky *et al*., 2001). Effect sizes were found to be consistent in the warm and cool seasons. Petroeschevsky *et al*. commented that the year-round effect of O_3 might reflect the relatively small degree of seasonal variation in O_3 levels observed in Brisbane. Mean 8-h avg O_3 (10a.m.-6p.m.) levels for the winter, spring, summer, and fall were 16.1ppb, 23.3ppb, 19.9ppb, and 16.7ppb, respectively.

For respiratory hospital admission studies, the largest, most significant associations with O_3 concentrations were observed when using short lag periods, in particular a 0-day lag (exposure on same day) and a 1-day lag (exposure on previous day). In the study of 16 Canadian cities by Burnett *et al*. (1997a), the strongest association between O_3 and respiratory hospitalisations was found at a 1-day lag. A decline in the magnitude and significance of the effect was seen with increasing days lagged for O_3. Anderson *et al*. (1997) investigated the association between O_3 and daily hospital admissions for COPD in five European cities. Lags up to 5 days were examined, and the largest risk estimates were found using 0- and 1-day lags. These results suggest that O_3 has a short-term effect on respiratory hospitalizations (USEPA, 2006).

The epidemiological evidence for cardiovascular morbidity is much more mixed than for respiratory morbidity, with only one of several U.S./Canadian studies showing statistically significant positive associations of cardiovascular hospitalizations with warm-season O_3 concentrations. Most of the available European and Australian studies, all of which conducted all-year O_3 analyses, did not find an association between short-term O_3 concentrations and cardiovascular hospitalizations. The USEPA (2006) concluded that the currently available evidence is inconclusive regarding an association between cardiovascular hospital admissions and ambient O_3 exposure. Based on the evidence from animal toxicology, human controlled exposure, and epidemiologic studies, the USEPA concludes that this generally limited body of evidence is highly suggestive that O_3 can directly and/or indirectly contribute to cardiovascular-related morbidity, but that much needs to be done to more fully substantiate links between ambient O_3 exposures and adverse cardiovascular outcomes (USEPA, 2006).

The findings of controlled human exposure studies show that the responses in humans exposed to ambient O_3 concentrations include: decreased inspiratory capacity; mild

bronchoconstriction; rapid, shallow breathing pattern during exercise; and symptoms of cough and pain on deep inspiration. Reflex inhibition of inspiration results in a decrease in forced vital capacity (FVC) and, in combination with mild bronchoconstriction, contributes to a decrease in the forced expiratory volume in 1 s (FEV1). In addition to physiological pulmonary responses and symptoms of breathing discomfort, O_3 exposure also results in airway hyperresponsiveness, inflammation, immune system activation, and epithelial injury. With repeated O_3 exposures over several days, spirometric and symptom responses become attenuated, but this tolerance is lost after about a week without exposure (USEPA, 2006).

Airway responsiveness also appears to be attenuated with repeated O_3 exposures, but less so than FEV1. Unlike spirometric and symptom responses, airway inflammation and small airways dysfunction may not become attenuated by repeated O_3 exposures. Healthy young adults exposed to O_3 concentrations ≥0.08ppm develop significant reversible, transient decrements in pulmonary function if minute ventilation (VE) or duration of exposure are increased sufficiently (USEPA, 2006). The pattern of FEV1 response appears to depend on the O_3 exposure profile. Triangular exposure profiles can potentially lead to greater FEV1 responses than square wave exposures at equivalent average O_3 doses. O_3-induced decrements in FEV1 do not appear to depend on gender, race, body surface area, height, lung size, or baseline FVC in healthy young adults. Healthy children experience similar spirometric responses but lesser symptoms from O_3 exposure relative to young adults. On average, spirometric and symptom responses to O_3 exposure appear to decline with increasing age beyond about 18 years of age (USEPA, 2006).

There is a large degree of inter-subject variability in physiologic and symptomatic responses of healthy adults exposed to O_3. However, responses tend to be reproducible within a given individual over a period of several months. With increasing O_3 concentration, the distribution of FEV1 decrements becomes asymmetrical, with a few individuals experiencing large decrements. There is a tendency for slightly increased spirometric responses in mild asthmatics and allergic rhinitics relative to healthy young adults. Spirometric responses in asthmatics appear to be affected by baseline lung function, i.e., responses increase with disease severity. With repeated daily O_3 exposures, spirometric responses of asthmatics become attenuated; however, airway responsiveness becomes increased in subjects with pre-existing allergic airway disease (with or without asthma). Possibly due to patient age, O_3 exposure does not appear to cause significant pulmonary function impairment or evidence of cardiovascular strain in patients with cardiovascular disease or chronic obstructive pulmonary disease relative to healthy subjects (USEPA, 2006).

Available information on recovery from O_3 exposure indicates that an initial phase of recovery in healthy individuals proceeds relatively rapidly, with acute spirometric and symptom responses resolving within about 2 to 4 h. Small residual lung function effects are almost completely resolved within 24h. Effects of O_3 on the small airways, assessed by persistent decrement in FEF25–75 and altered ventilation distribution, may be due in part to inflammation. Indeed, a prolonged recovery of residual spirometric decrements following the initial rapid recovery could be due to slowly resolving airway inflammation. In hyper-responsive individuals, this recovery takes longer (as much as 48 hours) to return to baseline values. Persistent spirometry changes observed for up to 48h post-exposure could plausibly be sustained by the inflammatory mediators. Cellular responses (e.g. release of immunomodulatory cytokines) appear to still be active as late as 20h post-exposure. More slowly developing inflammatory and cellular changes may persist for up to 48h, but the time course for these parameters in humans has not been explored fully (USEPA, 2006).

3.4.3 Long Term Effects

3.4.3.1 Mortality

A number of studies have evaluated the relationship between chronic O_3 exposure and mortality. In the Harvard Six City prospective cohort analysis mortality was not associated with long-term exposure to O_3 (Dockery *et al*., 1993). The range of O_3 concentrations across the six cities was small (19.7 to 28.0ppb in average 24-hr concentrations over the 7-year study period), which may have limited the power of the study to detect associations between mortality and O_3 levels (USEPA, 2006). In a reanalysis of data from the Harvard Six City prospective cohort study, the investigators replicated and validated the findings of the original studies, and the report included additional quantitative results beyond those available in the original report (Krewski *et al*., 2000). The effect estimate for the association between long-term O_3 concentrations (8.3ppb between the highest and lowest concentrations in the cities) and mortality was negative and nearly statistically significant (relative risk = 0.87, 95% CI: 0.76, 1.00).

The ACS study is based on health data from a large prospective cohort of approximately 500,000 adults and air quality data from about 150 U.S. cities. The initial report (Pope *et al*., 1995) focused on associations with fine particles and sulfates, for which significant associations had been reported in the earlier Harvard Six Cities study (Dockery *et al*., 1993). As part of the major reanalysis of these data, results for associations with other air pollutants were also reported, and the authors report that no significant associations were found between O_3 and all cause mortality (95% CI: 0.96-1.07). A significant association was reported for cardiopulmonary mortality (relative risk=1.08, 95% CI: 1.01, 1.16) (Krewski *et al*., 2000). For some specifications of O_3 exposure in the ACS study, there was an effect in the warm season, as there was in the reanalysis of the Harvard Six Cities study.

The ACS II study (Pope *et al*., 2002) reported results of associations with an extended data base to include 16 years of follow-up (compared with 8 years in the first report) and more recent air quality data in the analyses. Results are presented for full-year and summer season analyses, and show no evidence for a significant association between long-term exposure to O_3 and mortality. The effect estimates were not statistically significant for associations between long-term O= exposure and all-cause, cardiopulmonary, and lung cancer mortality (USEPA, 2006) in all year analyses. However, in the summer season, marginally significant associations were observed for cardiopulmonary mortality.

The Adventist Health and Smog (AHSMOG) cohort includes about 6,000 adults living in California. In two studies from this cohort, a significant association has been reported between long-term O_3 exposure and increased risk of lung cancer mortality among males only (Beeson *et al*., 1998; Abbey *et al*., 1999). No significant associations were reported between long-term O_3 exposure and mortality from all causes or cardiopulmonary causes. Due to the small numbers of lung cancer deaths (12 for males, 18 for females) and the precision of the effect estimate (i.e., the wide confidence intervals), the USEPA raised concerns about the plausibility of the reported association with lung cancer (USEPA, 2006).

The U.S. Veterans Cohort study (Lipfert *et al*., 2000b, 2003) of approximately 50,000 middle-aged males diagnosed with hypertension, reported some positive associations between mortality and peak O_3 exposures (95th percentile level for several years of data). The study included numerous analyses using subsets of exposure and mortality follow-up periods which spanned the years 1960 to 1996. In the results of analyses using deaths and O_3

exposure estimates concurrently across the study period, there were positive, statistically significant associations between peak O_3 and mortality, with a 9.4% excess risk (95% CI: 0.4, 18.4) per mean 95% percentile O3 (USEPA, 2006).

The USEPA (2006) concluded that the results from all-year analyses in the Harvard Six Cities and ACS cohorts provide no evidence for associations between long-term O_3 exposure and mortality, though the warm-season results in the reanalysis of the ACS cohort study suggest a potential association. Imprecise and inconclusive associations were reported in analyses for the AHSMOG cohort study. Significant associations between long-term O_3 exposure and mortality were only reported for the Veterans cohort study; however, this study used an indicator of peak O_3 concentrations and the cohort is also a rather specific subgroup of the U.S. population. Overall, the USEPA (2006) concluded that consistent associations have not been reported between long-term O_3 exposure and all-cause, cardiopulmonary or lung cancer mortality.

3.4.3.2 Morbidity

Several epidemiological studies have examined the relationship between lung function development and long-term O_3 exposure (USEPA, 2007). The most extensive and robust study of respiratory effects in relation to long-term air pollution exposures among children is the Children's Health Study carried out in 12 communities of southern California starting in 1993 (Avol *et al*., 2001; Gauderman *et al*., 2000, 2002, 2004a,b; Peters *et al*., 1999a,b). One study (Peters *et al*., 1999a) examined the relationship between long-term O_3 exposures and self reports of respiratory symptoms and asthma in a cross sectional analysis and found a limited relationship between outcomes of current asthma, bronchitis, cough and wheeze and a 40ppb increase in 1-hr max O_3 (USEPA, 2006). Another analysis (Peters *et al*., 1999b) examined the relationship between lung function at baseline and levels of air pollution in the community and reported evidence that annual mean O_3 levels were associated with decreases in FVC, FEV1, PEF and FEF25–75 (the latter two being statistically significant) among females but not males. In a separate study of 4th, 7th, and 10th grade students (Gauderman *et al*., 2000), a longitudinal analysis of lung function development over four years found no association with O_3 exposure. Subsequent studies by the same group (Gauderman *et al*., 2002, 2004a,b) led the authors to conclude that results provide little evidence that ambient O_3 at current levels is associated with chronic deficits in the rate of increase in growth-related lung function in children (USEPA, 2006).

Evidence for a significant relationship between long-term O_3 exposures and decrements in maximally attained lung function was reported in a nationwide study of first year Yale students (USEPA, 2006). Males had much larger effect estimates than females, which may have reflected higher outdoor activity levels and correspondingly higher O_3 exposures during childhood. A similar study (Kunzli *et al*., 1997; Tager *et al*., 1998) of college freshmen at University of California at Berkeley also reported significant effects of long-term O_3 exposures on lung function. In a comparison of students whose city of origin was either Los Angeles or San Francisco, long-term O_3 exposures were associated with significant changes in mid- and end-expiratory flow measures, which could be considered early indicators for pathologic changes that might progress to COPD (USEPA, 2007).

There have been a few studies investigating associations between long-term O_3 exposures and the onset of new cases of asthma (USEPA, 2006). The Adventist Health and Smog (AHSMOG) study cohort of 3,914 was drawn from non-smoking, non-Hispanic white adult Seventh Day Adventists living in California (Greer *et al*., 1993; McDonnell *et al*., 1999).

Subjects were surveyed in 1977, 1987, and 1992. During the ten-year follow-up in 1987, it was reported that the incidence of new asthma was 2.1% for males and 2.2% for females (Greer *et al*., 1993). A statistically significant relative risk of 3.12 (95% CI: 1.16, 5.85) per 10ppb increase in annual mean O_3 was observed in males, compared to a non-significant relative risk of 0.94 (95% CI: 0.65, 1.34) in females. In the 15-year follow-up in 1992, it was reported that 3.2% of eligible males and 4.3% of eligible females had developed adult asthma (McDonnell *et al*., 1999). For males, the relative risk of developing asthma was 2.27 (95% CI: 1.03, 4.87) per 30ppb increase in 8-hr average O_3, but there was no evidence of an association in females. The lack of an association in females does not necessarily mean there is no effect but may be due to differences in time-activity patterns in males and females, which could lead to greater misclassification of exposure in females. Consistency of results in the two studies with different follow-up times provides supportive evidence of an association between long-term O_3 exposure and asthma incidence in adult males; however, representativeness of this cohort to the general U.S. population may be limited (USEPA, 2007).

In a similar study of incident asthma among children (ages 9 to 16 at enrolment), annual surveys of 3,535 children initially without asthma were used to identify new-onset asthma cases as part of the Children's Health Study (McConnell *et al*., 2002). Six high-O_3 (75.4ppb mean 1-hr max over four years) and six low-O_3 (50.1ppb, mean 1-hr max) communities were identified where the children resided. There were 265 children who reported new-onset asthma during the follow-up period. Although asthma risk was no higher for all residents of the six high-O_3 communities versus the six low-O_3 communities, asthma risk was 3.3 times greater for children who played three or more sports as compared with children who played no sports within the high-O_3 communities. This association was absent in the communities with lower O_3 concentrations. No other pollutants were found to be associated with new-onset asthma (USEPA, 2006). Playing sports may result in extended outdoor activity and exposure occurring during periods when O_3 levels are higher. The sports activities would cause an increased ventilation rate, thus resulting in increased O_3 dose.

In summary the USEPA concluded that evidence from longitudinal studies that have examined the effect of chronic O_3 exposure on respiratory health outcomes have suggested in some cases that chronic exposure to O3 may be associated with seasonal declines in lung function or reduced lung function development, increases in inflammation, and development of asthma in children and adults (USEPA, 2007). Seasonal decrements or smaller increases in lung function measures have been reported in several studies however it remains uncertain to what extent these changes are transient. While there is supportive evidence from animal studies involving chronic exposures, large uncertainties still remain as to whether current ambient levels and exposure patterns might cause these same effects in human populations. The USEPA also concluded that epidemiological studies of new asthma development and longer-term lung function declines remain inconclusive at present (USEPA, 2006).

The USEPA concluded that there is limited evidence from human studies for long-term O_3-induced effects on lung function. Epidemiological studies have provided only inconclusive evidence for either mortality or morbidity effects of long-term O_3 exposure (USEPA, 2006). Several longitudinal epidemioloical studies have evaluated associations between long-term O_3 exposures and morbidity and mortality and suggest that these long-term exposures may be related to changes in lung function in children however little evidence is available to support a relationship between chronic O_3 exposure and mortality or lung cancer incidence (USEPA, 2006).

The USEPA (2006) concluded that evidence from animal toxicology studies strongly suggests that chronic O_3 exposure is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodelling leading to apparent irreversible changes. Such structural changes and compromised pulmonary function caused by persistent inflammation may exacerbate the progression and development of chronic lung disease. Together with the limited evidence available from epidemiological studies, these findings offer some insight into potential biological mechanisms for suggested associations between long-term or seasonal exposures to O_3 and reduced lung function development in children which have been observed in epidemiological studies (USEPA, 2006).

3.4.4 Australian Studies

A number of Australian studies investigating the health effects of ozone have been reported since the last NEPM review. The "Preliminary Work on Ozone for the Review of the Ambient Air Quality NEPM", (NEPC 2005) documented and discussed a series of Australian studies.

3.4.4.1 Mortality

Studies in Australian cities investigating the effects of ozone exposure on mortality rates have reported mixed results. Associations between 1, 4 and 8 hours ozone levels and total mortality were reported in Brisbane (Simpson *et al*. 1997), Melbourne (Simpson *et al*. 2000) and Sydney (Morgan *et al*., 1998b), but a later multi-city study reported no association (Simpson *et al*. 2005b). Associations between 4 hour and 8 hour ozone levels were reported in studies in Perth (Hinwood *et al*. 2004) and the multi-city and Melbourne studies mentioned above, but not in the Brisbane and Sydney studies. Only the Perth study reported a significant association between ozone exposure and cardiovascular mortality.

3.4.4.2 Respiratory Effects

Mixed results were reported for associations between ozone levels and hospitalization for respiratory symptoms. Two multi-city studies (Barnett *et al*. 2005, Simpson *et al*. 2005a), reported positive associations between increases in ozone levels of 0.001ppm and respiratory admissions. This association was only demonstrated in one of the studies in the warm season (Barnett *et al*. 2005). The Victorian EPA (2001) reported increases in hospital admissions for respiratory and asthma with increases in ozone levels, with larger increases reported in the warm season.

An Australian population study of childhood emergency presentations for asthma in Melbourne regions reported mixed results with a positive significant (non-linear) relationship with ozone concentrations in the Western and South/South Eastern regions, but not in other regions (Erbas *et al*. 2005).

An 11 month longitudinal panel study of 125 primary school children with a history of wheeze in Sydney, reported no associations between ambient ozone concentrations and respiratory symptoms, asthma medication use, and doctor visits for asthma (Jalaludin *et al*. 2004).

Another recent panel study in Perth found an association between ozone and raised body temperature on the day of onset of upper respiratory illness. Incidence of cough was also increased, but not significantly (Rodriguez *et al*. 2007). Similar panel studies in the US have

demonstrated that increases in ozone impacts on respiratory symptoms. In Connecticut a 0.05ppm increase in 1-hour ozone was associated with a 35% increase in wheeze, and inner city children with asthma had 16% increased risk for morning symptoms for each 0.015ppm increase in ozone (Gent *et al*. 2003, Mortimer *et al*. 2002).

The threshold based on respiratory effects in young, healthy, non-smoking males was estimated at 0.075ppm for a four hour threshold by the Woolcock Report (2003), supporting similar estimates of a threshold level by major overseas agencies (Woolcock Institute of Medical Research 2003).

3.4.4.3 Cardiovascular effects

Mixed results were also reported for associations between ozone levels and hospitalization for respiratory symptoms, with only Simpson *et al*. (2005) reporting an association between ozone levels and hospital admissions for cardiovascular admissions. A study of elderly people's emergency department attendances in Sydney found no effect of ozone on the rate of attendances for cardiovascular conditions, (Jalaludin *et al*., 2006).

Table 3.3: Summary of effect estimates of short-term increments in ozone

Health Outcome	Effect Estimate (95% CI)	Increment in O_3 *	City	Reference
Mortality				
All-cause	2.4%(0.8-4)	0.01ppm 8hr, lag0	Brisbane	(Simpson *et al*. 1997)
	2%(0.4-3.7)	0.03ppm 1hr, lag0	Sydney	(Morgan *et al*. 1998b)
	0.3%[1, 2]	0.001ppm 1-hr, lag0-2	Melbourne	(Simpson *et al*. 2000)
	Nil		B/M/P/S[3]	(Simpson *et al*. 2005b)
Cardiovascular	2% NS	0.01ppm 8hr, lag0	Brisbane	(Simpson *et al*. 1997)
	2.5%NS	0.03ppm 1hr, lag0	Sydney	(Morgan *et al*. 1998b)
	0.45%[4]	0.001ppm 8hr, lag0	Perth	(Hinwood *et al*. 2004)
	Nil		B/M/P/S[3]	(Simpson *et al*. 2005b)
Respiratory	3.9% NS	0.01ppm 8hr, lag0	Brisbane	(Simpson *et al*. 1997)
	Nil		Sydney	(Morgan *et al*. 1998b)
	0.5%[5]	0.001ppm 4hr, same day	Melbourne	(Simpson *et al*. 2000)
	~0.6%[4]	0.001ppm 8hr, lag3	Perth	(Hinwood *et al*. 2004)
	0.25(0.03-0.48)	0.001ppm 4hr, lag0-1	B/M/P/S[3]	(Simpson *et al*. 2005b)
Hospitalisation				
Cardiac	2.5% NS [6]	0.03ppm 1hr, lag0	Sydney	(Morgan *et al*. 1998a)
	Nil		Brisbane	(Petroeschevsky *et al* 2001)
	0.09%(0.01-0.17) [7]	0.001ppm 4hr, lag3	B/M/P/S[3]	(Simpson *et al*. 2005a)
	Nil		7 cities[8]	(Barnett *et al*. 2006)
	Nil		Perth	(Hinwood *et al*. 2006)
Respiratory	Nil		Sydney	(Morgan *et al*. 1998a)
	2.3%(0.3-4.3) [9]	0.01ppm 8hr, lag2	Brisbane	(Petroeschevsky *et al* 2001)
	0.14%(0.01-0.26)[6,10]	0.001ppm 4hr, lag3	B/M/P/S[3]	(Simpson *et al*. 2005a)
	3.5%(1.8-5.2) [2,10]	0.001ppm	7 cities[8]	(Barnett *et al*. 2005)

		1-hr, lag0-1		
	Nil		Perth	(Hinwood *et al*. 2006)

NS –not significant

* Increment of ozone for which the effect was estimated, including averaging period (1, 4 or 8 hour maximum) and whether it occurred on the same day as the effect (lag0), previous day (lag1) or an average of same and previous days (lag01=same+previous, lag02=same&2 previous)

[1] Study reports per 1μg/m^3 increase: 0.16% (0.06-0.26)

[2] Warm season only

[3] Brisbane, Melbourne, Perth, Sydney

[4] Odds ratio, significant, CI not given

[5] Study reports per 1μg/m^3 increase: 0.27% (0.07-0.47). Effect was higher in warm season (0.35%)

[6] Elderly: >65years

[7] Adults <65years

[8] Brisbane, Canberra, Melbourne, Perth, Sydney & Auckland, Christchurch NZ

[9] Larger effects seen in ages >15years and for asthma

[10] Asthma+COPD - similar estimates for same day 4hr & 1hr lag3

[11] children 1-4years

Of the birth studies undertaken in Australia, a study in Brisbane reported exposure to ozone during trimester one was associated with an increased risk of pre-term birth with an odds ratio of 1.26 (95%, 1.10-1.45%) (Hansen *et al*. 2006). A similar finding, limited to pregnancies conceived in the spring, was demonstrated in Sydney, (Jalaludin *et al*. 2007). Another study in Brisbane reported that there was no strong evidence of an association between ozone levels during pregnancy and sub-optimal foetal growth (Hansen *et al*., 2007). A study of 'small for gestational age' babies over a two year period in Sydney did not report any association between birth weight and ozone levels (Mannes *et al*. 2005).

3.4.5 Findings of the review of the ozone health evidence

Recent studies have supported the findings of the preliminary work done for the review of the ozone standards. Exposure to ozone is associated with increases in daily mortality and hospital admissions and emergency department attendances. These associations have been found with exposures to 1-hour, 4-hour and 8-hour exposure times. The results of the Australian studies support those found in international studies.

Exposure to ozone in Australian cities varies and given the pattern of ozone peaks a set of standards covering 1-hour, 4-hour and 8-hour exposure times is appropriate for Australia. This finding is consistent with the recommendations from the preliminary work for ozone (NEPC, 2005).

3.4.5.1 Implications of the health evidence for the ozone NEPM standard

Based on the outcomes of the preliminary work on ozone, the most recent reviews from the international agencies and the results of recent epidemiological studies conducted in Australia finding health effects below the current NEPM standards, implications for the ozone standard are that there are still significant health effects observed at levels below the current one hour and 4 hour standards. The health evidence supports the findings of the preliminary work on ozone to introduce an 8 hour standard to the existing averaging periods. Emerging evidence suggests that health effects are observed in longer averaging periods such as 8 hours.

3.5 Sulfur Dioxide

3.5.1 Introduction

In recent years the health effects of sulfur dioxide (SO_2) linked to ambient exposures have been well studied and reviewed by international agencies such as the USEPA (2008b) the WHO (2006) and California EPA (OEHHA, 2000). A review of the SO_2 standard in the AAQ NEPM was also conducted in 2004 by NEPC (NEPC, 2004). As part of this review the health effects of SO_2 were reviewed with a strong focus on studies conducted with short-term exposure (15 mins to 1-hour). A comprehensive evaluation of the evidence relating to SO_2 in ambient air and impacts on health is contained in AAQ NEPM Health Reviews 2009.

A large number of population-based epidemiological studies have reported a link between short term SO_2 exposure and daily mortality and respiratory and cardiovascular effects. The associations persist when other pollutants, such as particles, are controlled for. The epidemiological evidence is supported by controlled human exposure studies and animal toxicology studies.

The strongest evidence comes from controlled human exposure studies examining short term exposure to SO_2 and respiratory effects. These studies have exposed volunteers to SO_2 for periods ranging from 5–10 min up to one hour. Adverse effects, such as sneezing or shortness of breath, occur within the first few minutes after inhalation and are not changed by further exposure. The effects are greater when the person is exercising, and are most pronounced in people with asthma and other respiratory conditions such as COPD, and particularly in exercising asthmatics.

3.5.2 Short term exposure

3.5.2.1 Mortality

A large number of epidemiological studies in cities in various parts of the world, including the United States, Canada and Europe, have reported associations between exposure to ambient levels of sulfur dioxide and increases in all-cause (non-accidental) and respiratory and cardiovascular mortality, often at mean 24-h average levels of <10ppb (Biggeri *et al*. 2005; Samet *et al*., 2000a; Dominici *et al*., 2003; Burnett *et al*., 1998a, 2000, 2004; Katsouyanni *et al*. 1997, 2006; Samoli *et al*., 2001, 2003; US EPA, 2008b; Stieb *et al*. 2002, 2003). The mortality effect estimates for cardiovascular and respiratory causes are generally larger than for all-cause mortality (Zmirou *et al*., 1998), and the effect estimates for respiratory mortality are larger than the cardiovascular mortality, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. The mortality effect estimates from the multipollutant models in the multicity studies suggest some extent of confounding between SO_2 and particles and/or NO_2 (USEPA, 2008b).

An association between exposure to ambient levels of sulfur dioxide and increases in mortality is supported by evidence from intervention studies. For example, a sudden change in regulation in Hong Kong, in July 1990, resulted in a restriction that required all power plants and road vehicles to use fuel oil with a sulfur content of not more than 0.5% by weight. Sulfur dioxide levels after the intervention declined by about 50% (from 44 to 21 $\mu g/m^3$) but PM_{10} levels did not change. The average annual trend in death rate significantly declined after the intervention for all-cause (2.1%), respiratory (3.9%) and cardiovascular mortality (2.0%) (Hedley *et al*. 2002). SO_2 was most consistently associated

with mortality, whereas the association of PM_{10} with mortality was only marginal, further supporting the case for SO_2 being more influential than particles, at least in Hong Kong (Wong *et al*. 2001). Thus, the Hong Kong case study seems to suggest that a reduction in sulphur dioxide (or other pollutants associated with sulfur-rich fuel) leads to an immediate reduction in deaths (WHO, 2006).

3.5.2.2 Respiratory symptoms and diseases

The epidemiological evidence, supported by controlled human exposure studies and a limited number of animal toxicological studies conducted at near ambient concentrations, indicate an association between short-term exposure to SO_2 and several measures of respiratory health, including respiratory symptoms, inflammation, and airway hyperreponsiveness (Hoek and Brunekreef, 1993; Peters *et al*., 1996a; Roemer *et al*., 1993; Segala *et al*., 1998; Timonen and Pekkanen, 1997Mortimer *et al*., 2002; Schildcrout *et al*., 2006; Schwartz *et al*., 1994; USEPA 2008b).

The epidemiological evidence further indicates that the SO_2-related respiratory effects (≥ 1-h, generally 24-h average) are more pronounced in asthmatic children and older adults (65+ years). In the limited number of studies that examined potential confounding by copollutants through multipollutant models, the SO_2 effect was generally found to be robust after adjusting for particles and other copollutants (USEPA, 2008b).

A number of intervention studies provide further evidence of an association between SO_2 and respiratory morbidity (USEPA, 2008b). The Hong Kong "intervention" event described earlier compared the effects of reducing SO_2 (up to 80% in polluted districts) and sulphate (38% in polluted districts) levels on bronchial responsiveness in primary school children living in two districts (polluted and less polluted). The authors found a greater decline in bronchial hyperreactivity and bronchial reactivity in schoolchildren in the polluted than in the less polluted district (Wong *et al*. 1998). Another study reported a significant decline in symptoms of cough, sore throat, phlegm, and wheezing in children from the polluted compared with the unpolluted district in Hong Kong (Peters *et al*. 1996b).

The strongest evidence for a causal relationship between respiratory morbidity and short-term exposure to SO_2 comes from human clinical studies reporting respiratory symptoms and decreased lung function following peak exposures of 5–10min duration to SO_2. The exact duration is not critical, however, because responses occur very rapidly, within the first few minutes from commencement of inhalation; continuing the exposure further does not increase the effects. These effects have been observed consistently across studies involving mild to moderate asthmatics during exercise. Statistically significant decrements in lung function accompanied by respiratory symptoms including wheeze, chest tightness and shortness of breath have been clearly demonstrated following exposure to 0.4–0.6ppm SO_2. Although studies have not reported statistically significant respiratory effects following exposure to 0.2–0.3ppm SO_2, some asthmatic subjects (5–30%) have been shown to experience moderate to large decrements in lung function at these exposure concentrations (USEPA, 2008b; WHO, 2006).

Such effects are enhanced by exercise, which increases the volume of air inspired, thereby allowing sulfur dioxide to penetrate further into the respiratory tract. An acute effect of short-term exposure at rest to 0.2ppm sulfur dioxide is a change in heart rate variability, in which normal young adults responded with small but statistically significant increases in both high and low frequency power, while asthmatic subjects responded with decreases in

these parameters of comparable magnitude. A wide range of sensitivity has been demonstrated, both among normal individuals and among those with asthma, who form the most sensitive group for pulmonary function changes. Continuous exposure–response relationships, without any clearly defined threshold, are evident (WHO, 2006).

From the information published to date, the overall conclusion is that the minimum concentration evoking changes in lung function in exercising asthmatics is of the order of 400ppb, although there is the one example of small changes in airway resistance in two sensitive subjects at 100ppb (WHO, 2006). In evaluating this further, judgements are required regarding the clinical significance of such effects, the extent to which particularly sensitive subjects have been represented in the studies, the practical relevance of the enforced exercise required to enhance the effects, and how to relate the short (10- to 15-minute) exposures to the more usual hourly average monitoring data (WHO, 2006).

3.5.2.3 Cardiovascular effects

Recent epidemiological studies have examined the association between air pollution and cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV), incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial infarctions (MI), and emergency department visits and hospitalizations due to cardiovascular causes. The epidemiologic evidence from studies of the effect of SO_2 on ICD-recorded arrhythmias, blood pressure and blood markers of cardiovascular risk failed to provide consistent evidence to suggest a role for SO_2 in cardiovascular disease development. Many researchers were unable to distinguish the effect of SO_2 from correlated copollutants while others reported a reduction in the SO_2 effect in two-pollutant models (USEPA, 2008b).

Tunnicliffe *et al*. (2001) measured cardiac function associated with acute exposure to SO_2 in a controlled human exposure study involving 12 normal and 12 asthmatic young adults. Exposures were of 1-hour duration, double blind, in random order, >2 weeks apart, and with clean air and 200ppb sulfur dioxide. The sulfur dioxide exposures were associated with statistically significant increases in high frequency (HF) and low frequency (LF) power in the normal subjects, and reductions in HF and LF of comparable magnitude in the asthmatic subjects. No pulmonary function changes or symptom frequency changes were observed in either group. These results suggest that sulfur dioxide exposures at concentrations frequently encountered during air pollution episodes can influence the autonomic nervous system. This may help in elucidating the mechanisms involved in the induction of bronchoconstriction and the cardiovascular effects of ambient air pollution (WHO, 2006).

Although biologically plausible modes of action that could explain short-term SO_2 effects on the cardiovascular system have been identified, consideration of these modes of action in light of findings from additional animal toxicological, human clinical and epidemiological studies led the USEPA to the conclusion that the evidence as a whole is inadequate to infer a causal relationship (USEPA, 2008b). Specifically, evidence from human clinical and epidemiological studies of HRV in healthy persons as well as persons with asthma or cardiovascular disease was inconsistent and did not support an effect of SO_2 on the autonomic nervous system, despite some positive findings.

Several studies have observed positive associations between ambient SO_2 concentrations and emergency department visits or hospital admissions for cardiovascular diseases (e.g., all cardiovascular diseases, cardiac diseases, cerebrovascular diseases) particularly among individuals 65+ years of age, but results are not consistent across studies. The strongest

evidence comes from a large multicity study conducted in Spain (Ballester *et al*. 2006) that observed statistically significant positive associations between ambient SO_2 and cardiovascular disease admissions, however, the SO_2 effect was found to diminish by half with PM_{10} and CO adjustment. In an Australian study, Jalaludin *et al*. (2006) reported a 3% excess risk in cardiovascular disease hospital admissions per 0.75ppb incremental change in 24-h average SO_2 in single-pollutant models, which was reduced to null when CO was included. See more on associations between SO_2 and emergency department visits and hospitalizations below.

3.5.2.4 Hospital admissions and emergency department attendances

A large body of epidemiological studies generally report consistent and robust associations between ambient SO_2 concentrations and emergency department visits and hospitalizations for all respiratory causes, particularly among children and older adults (65+ years), and for asthma and chronic obstructive pulmonary disease (COPD) (USEPA, 2008b). Mean 24-h average SO_2 levels in these studies ranged from 1 to 30ppb, with maximum values ranging from 12 to 75ppb (e.g. Barnett *et al*. 2005; Sunyer *et al*., 1997, 2003; Anderson *et al*., 1998; Hajat *et al*., 1999; Schouten *et al*., 1996; Spix *et al*., 1998; Wong *et al*., 1999a).

Some studies report greater increase in emergency department visits and hospitalizations for respiratory illnesses during the summer months (Anderson *et al*., 1998; Hajat *et al*., 1999; Schouten *et al*., 1996; Spix *et al*., 1998; Wong *et al*., 1999a), and others found the associations, with similar increases in SO_2, to be greater in winter (Castellsague *et al*., 1995; Tenias *et al*., 1998; Wong *et al*., 2002c; Vigotti *et al*., 1996; Walters *et al*., 1994). Warmer months were more likely to show evidence of an association with adverse respiratory outcomes in children, while older adults appeared more likely to be affected during the cooler months.

In a case-crossover study of air pollution and child respiratory health undertaken in five Australian and two New Zealand cities, Barnett *et al*. (2005) found a statistically significant increase in hospital admissions and SO_2 with an interquartile range of 5.4ppb for 1-hour SO_2. The ambient levels recorded during the study included: SO_2 1 hour mean (3 cities) 7.1ppb, range of means 3.7 to 10.1ppb; 24 hour mean (4 cities) 4.5ppb range of means 0.9 to 4.3ppb. In the 1–4 year age group there was evidence of seasonal impacts on pneumonia and acute bronchitis admissions for SO_2 (May to October 4.9% increase 95% CI, 0.6–10.8%, November to April 10.4% increase 95% CI, 2.1–19.4%) (Barnett *et al*. 2005).

3.5.3 Long term exposure

3.5.3.1 Mortality

Epidemiological evidence on the effect of long-term exposure to SO_2 on mortality is limited, and according to the US EPA (2008b), is inadequate to infer a causal relationship at this time.

Overall, reanalysis of results from two major U.S. epidemiological studies (Pope *et al*. 1995; Dockery *et al*., 1993) observe an association between long-term exposure to SO_2 or sulfur-containing particulate air pollution and mortality (Pope *et al*. 2002; Krewski *et al*. 2000; Jerrett *et al*., 2003a; Elliott *et al*. 2007). However, several other U.S. and European cohort studies did not observe an association (Abbey *et al*. 1999; Lipfert *et al*. 2000b; Nafstad *et al*. 2004; Filleul *et al*. 2005; Beelen *et al*. 2008). The lack of consistency across studies, inability to distinguish potential confounding by copollutants, and uncertainties regarding the geographic scale of analysis, limit the interpretation of a causal relationship (USEPA, 2008b).

Evidence from epidemiological studies shows positive and statistically significant associations between a reduction in life expectancy and long-term exposure to particulate pollution ($PM_{2.5}$ and sulfate) and SO_2. This was noted in the Committee on the Medical Effects of Air Pollutants (COMEAP) Statement and Report on the Long Term Effects of Particles on Mortality (Committee on the Medical Effects of Air Pollutants, 2001b). Re-analysis of these studies by the US Health Effects Institute has confirmed the initial findings and has extended them by showing that the reduction in life expectancy is due to increased deaths from cardiovascular rather than respiratory disease, a most important finding (Curtin University, 2008).

3.5.3.2 Morbidity

The results of studies examining the association between long-term exposure to SO_2 and respiratory morbidity are generally inconsistent. Cross-sectional studies conducted in New South Wales in the Hunter and Illawarra regions found no association between annual average levels of sulfur dioxide and prevalence of asthma in children (Henry *et al*, 1991) and chest colds and respiratory symptoms such as cough and wheeze (Lewis *et al*, 1998). Studies identified by the USEPA (2008b) that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children. In the limited number of studies examining the SO_2 associations with lung function, results were generally mixed.

A major consideration in evaluating SO_2-related health effects and long-term exposure is the high correlation, and potential confounding, among the copollutant levels observed, particularly between long-term average particle concentrations and SO_2. The USEPA (2008b) concluded in its review that the overall epidemiological evidence on the respiratory effects of long-term exposure to SO_2 is inadequate to infer a causal relationship. The available toxicological and epidemiological evidence to assess the effect of long-term exposure to SO_2 on cardiovascular health is also too limited to make any conclusions at this time.

3.5.3.3 Birth outcomes

A number of studies have reported associations between exposure to SO_2 and low birth weight and premature birth (Sram *et al*., 2005; Dugandzic *et al*., 2006; Jalaludin *et al* 2007). A study of 123,840 singleton births of over 20 weeks' gestation in Sydney, between 1998 and 2000, found that 4.9% of babies were born at less than 37 weeks gestation. The mean of the one hour maximum SO_2 levels was 3.6ppb. SO_2 level in early pregnancy had a large adverse impact on gestational age in those infants conceived in autumn and winter for a 1ppb increase in SO_2. The authors caution that SO_2 appears to be an important pollutant, despite SO_2 levels in Sydney being well below the national standard, with vehicular traffic being the primary source and it is conceivable that SO_2 is a marker for traffic related air pollutants in the study (Jalaludin *et al* 2007). A Canadian study found that first trimester exposures in the highest quartile for SO_2 and PM_{10} suggested an increased risk of delivering a low birth weight infant (Dugandzic *et al*., 2006). Leem *et al*. (2006) also found an association between low birth weight and low levels of air pollutants including SO_2 in Korea. In the USA, a time-series study undertaken by Sagiv *et al*. (2005) found evidence of an increase in preterm birth risk with exposure to PM_{10} and SO_2, which were consistent with prior investigations of spatial contrasts.

The US EPA (2008b) concluded that while the epidemiological studies on birth outcomes have observed positive associations between SO_2 exposure and low birth weight;

toxicological studies provide very little biological plausibility for the effects. The limited number of studies, inconsistent results across trimesters of pregnancy, and the lack of evidence regarding confounding by copollutants limit the interpretation of these studies and make it difficult to draw conclusions regarding the effect of SO_2 on birth outcomes.

3.5.4 Threshhold for effects and sensitive groups

The reported associations between exposure to SO_2 and adverse health outcomes from overseas studies relate to a range of 24 hour average and daily one hour maximum exposure levels including very low levels, suggesting that there may be no threshold for the health effects associated with exposures to sulfur dioxide in sensitive subgroups of the population.

Asthmatics appear to be the most susceptible group to the effects of sulfur dioxide (Streeton, 1997). The elderly are also a susceptible population as they have reduced respiratory reserve as a result of the ageing process. This is also often exacerbated by pre-existing cardio-respiratory disease.

The studies reviewed indicate that short-term exposures of 5-15 minutes to sulphur dioxide are associated with a dose-response effect on lung function of exercising individuals with asthma. The controlled exposure study by Linn *et al* (1987) in exercising individuals with asthma is indicative of a LOAEL of 0.2ppm for a 15 minute exposure period for this small sample of susceptible individuals. Responses to brief short-term exposures to sulfur dioxide are immediate and do not appear to worsen after longer exposure periods.

Epidemiological studies that have examined longer exposure times (one hour maximum, 24 hour and annual average) indicate that other susceptible populations, in addition to people with asthma, may include those with chronic obstructive pulmonary disease and existing cardiovascular disease, children and the elderly. Compared to healthy adults, children are generally more sensitive to air pollutants as their exposure is generally higher. The reasons for this are that children inhale more air per minute and have a larger contact lung surface area relative to their size compared to adults. Other factors that increase the potential for exposure in children are that they generally spend more time outdoors and exercising.

3.5.5 Findings of the review of the sulfur dioxide health evidence

Epidemiological studies have shown associations between ambient levels of SO_2 and increased mortality. The effects estimates from several multicity studies suggest a stronger association in levels of SO_2 (standardized for each 10ppb increase in 24-hour average) with respiratory mortality compared to cardiovascular mortality.

Exposure to SO_2 is also associated with increased respiratory and cardiovascular morbidity, including increased hospital admissions for respiratory and cardiovascular diseases, especially among asthmatics, the very young children and the elderly. Increased levels of SO_2 during pregnancy have also been associated with low birth weight and premature birth. Changes to autonomic function such as heart rate variability provide some plausibility to the results of studies showing increases in cardiovascular hospital admissions at low levels of SO_2 especially among the elderly and those with pre-existing cardiovascular disease.

Asthmatics have been identified as the most susceptible group to respiratory effects of SO_2. Australia has one of the highest asthma rates in the world. Among asthmatics, both the magnitude of SO_2-induced decrements in lung function and the percent of individuals

affected have consistently been shown to increase with increasing exposure to SO_2 concentrations between 0.2 and 1.0ppm. These results represent the response to SO_2 among groups of relatively healthy asthmatics and cannot necessarily be extrapolated to the most sensitive asthmatics in the population who are likely more susceptible to the respiratory effects of exposure to SO_2 (USEPA, 2008b).

3.5.5.1 Implications of the health evidence for the sulfur dioxide NEPM standard

The reported associations between exposure to SO_2 and adverse health outcomes from overseas studies relate to a range of 24 hour average and daily one hour maximum exposure levels including very low levels, suggesting that there may be no threshold for the health effects associated with exposures to sulfur dioxide in sensitive subgroups of the population.

The results of studies conducted since the NEPM was made in 1998 show adverse health outcomes below the current standards and Australia has a very large susceptible group.

3.6 Lead

3.6.1 Introduction

Lead is associated with a wide range of adverse health effects including effects on the blood, central nervous system, cardiovascular system, immune system and the kidneys. A significant proportion of lead that is inhaled can accumulate in the body. Children are the group most susceptible to the adverse health effects of lead, due to both higher likelihood of exposure via the ingestion pathway and because of their developing bodies. In the past 30 years, recommendations for limiting exposure to lead in the community have been largely driven by the need to protect children from the effects of lead on the developing brain.

- Lead differs from other criteria air pollutants in that it is both persistent in the environment and has multiple exposure pathways these being mainly air, water and soil. Blood lead levels are the key biomarker of current and recent lead exposure, and may also be a reasonably good indicator of lead body burden.
- Children remain the group most susceptible to adverse health effects of lead. Evidence has emerged for neurological health effects at blood lead levels less than 10µg/dL, with some studies reporting adverse effects as low as 2µg/dL. Effects measured include lowering of IQ and delinquency. Evidence has also increased for adverse neurological health effects in adults.
- Strong evidence exists for a causal relationship between lead and increased blood pressure or hypertension in adults at blood lead levels less than 10µg/dL. Some evidence exists for an association between lead and cardiovascular morbidity and mortality, but results are inconclusive at this stage. Renal function impairment in adults, measured as elevated serum creatinine and glomerular filtration rate (GFR) has been reported at blood lead levels between 2 and 10µg/dL in studies with adults in Europe and America.

The most recent review of lead (Pb) was conducted by the USEPA and completed in 2006. The review built on the findings of earlier reviews and identified a number of new epidemiological and toxicological studies that have been conducted since the previous reviews.

3.6.2 Epidemiological studies

3.6.2.1 Cognitive Function

The USEPA identified a number of studies that investigated the effects of Pb on cognitive function. These studies used a range of measures of cognitive function including;

- intelligence quotient or IQ score
- academic achievement
- specific cognitive abilities, e.g. attention, executive functions, language, memory, learning, and visuospatial processing.

Lead effects on human neurocognitive ability have been assessed in epidemiological studies largely by use of age-appropriate, standardized IQ tests. There is no direct parallel to IQ tests for nonhuman primates or rodents. However, in animals a wide variety of tests that assess attention, learning, and memory suggests that Pb exposure results in a global deficit in functioning, just as it is indicated by decrements in IQ scores in children (Rice, 1996).

The USEPA identified numerous well-conducted longitudinal cohort and cross-sectional studies that evaluated various study populations in several different countries have consistently found Pb-related IQ deficits from infancy through at least early school age. Several recent epidemiological studies have observed significant Pb-induced IQ decrements in children with peak blood Pb levels <10 µg/dL (e.g., Canfield *et al*., 2003a; Lanphear *et al*., 2005) and, in some cases, possibly below 5 µg/dL (Bellinger and Needleman, 2003; Téllez-Rojo *et al*., 2006). The most compelling evidence for effects below 10µg/dL, as well as a nonlinear relationship between blood Pb levels and IQ, comes from the international pooled analysis of seven prospective cohort studies (n = 1,333) by Lanphear *et al*. (2005). The slope for Pb effects on IQ was steeper at lower blood-Pb levels, as indicated by the cubic spline function, the loglinear model, and the piece-wise linear model. The shape of the spline function indicated that the steepest declines in IQ were at blood-Pb concentrations <10µg/dL. Based on stratified analyses using two cut points, a maximal blood-Pb of 7.5 and 10µg/dL, the effect estimate for children with maximal blood-Pb levels <7.5µg/dL was significantly greater than for those with a maximal blood-Pb <7.5µg/dL. Thus, recent epidemiological evidence is highly indicative of Pb induced neurocognitive deficits in children at blood Pb levels below 10 µg/dL and, possibly, as low as 5 µg/dL.

Other recent studies of the association of Pb with IQ in children with low Pb exposures have consistently observed effects at blood-Pb concentrations below 10µg/dL. Most notably, the large international pooled analysis of 1,333 children from seven different cohorts by Lanphear *et al*. (2005) estimated a decline of 6.2 points (95% CI: 3.8, 8.6) in full scale IQ for an increase in concurrent blood-Pb level from 1 to 10µg/dL. This study included 1,333 children from studies in America, Mexico, Australia and Europe. This effect estimate was comparable to the 7.4 point decrement in IQ for an increase in lifetime mean blood Pb levels up to 10µg/dL observed in the Rochester study (Canfield *et al*. 2003), as well as other studies reviewed above.

A common observation among some of these studies of low-level Pb exposure is a non-linear dose-response relationship between blood Pb and neurodevelopmental outcomes. The USEPA (2006) concluded that although this may seem at odds with certain fundamental toxicological concepts, it is possible that the initial neurodevelopmental lesions seen at lower Pb levels may be disrupting different biological mechanisms (e.g. early developmental

processes in the central nervous system) than the more severe effects of high Pb exposures that result in symptomatic poisoning and frank mental retardation.

Another global measure of cognitive function is academic achievement. Studies have focused on the effect of Pb on school performance, including reading, math, spelling, and handwriting. Lanphear *et al*. (2000) examined the relationship between blood-Pb levels and a standardized measure of academic achievement among 4,853 NHANES III children, aged 6 to 16 years (geometric mean blood-Pb of 1.9µg/dL). In analyses stratified by blood-Pb levels, statistically significant inverse relationships between blood-Pb levels and performance for both Reading and Arithmetic subtests were found for children with concurrent blood-Pb concentrations <5µg/dL. However, possible attribution of the observed associations of decrements in WRAT-R scores to earlier (but unmeasured) likely somewhat higher peak blood-Pb concentrations cannot be ruled out.

Several other epidemiological studies observed inverse associations between exposure to Pb and academic achievement, for the endpoints noted above as well as class rankings and high school graduation rates. One study examined 533 girls aged 6 to 12 years (mean blood Pb level of 8.1µg/dL) in Riyadh, Saudi Arabia and observed that, in a subset of students with blood-Pb levels <10µg/dL, class rank percentile was statistically significantly associated with blood-Pb levels (Al-Saleh *et al*., 2001).

In a study in Torreón, Mexico, a significant inverse relationship was found between blood-Pb concentrations and math and vocabulary scores in 594 second graders (mean blood Pb of 11.4µg/dL). In segmented regression analyses, slopes for blood Pb associations with vocabulary and math scores were significantly steeper below 10 µg/dL than above (Téllez-Rojo *et al*., 2006). Associations between Pb exposure and academic achievement observed in the noted studies were significant even after adjusting for IQ, suggesting that Pb-sensitive neuropsychological processing and learning factors not reflected by global intelligence indices might contribute to reduced performance on academic tasks (USEPA, 2006). In addition to IQ and academic achievement, epidemiological studies have evaluated Pb effects on specific cognitive abilities, e.g., attention, executive functions, language, memory, learning, and visuospatial processing. Results from these studies are most comparable to those experimental animal studies examining Pb effects on learning ability, memory, and attention.

In the large NHANES III study, children aged 6 to 16 years with concurrent blood Pb <5 µg/dL exhibited significant Pb-related decrements in Arithmetic and Reading scores (Lanphear *et al*., 2000). Inverse relationships between exposure to Pb and attentional behaviours and executive function were also observed in cohorts where >80% of the children had blood Pb levels <10µg/dL (Canfield *et al*., 2003b; Stiles and Bellinger, 1993). Other studies have also found significant Pb-induced impairments of neuromotor function (Després *et al*., 2005) and hearing (Osman *et al*., 1999; Schwartz and Otto, 1987, 1991) in children with blood-Pb levels <10µg/dL.

Collectively, these studies most clearly indicate that Pb is associated with various neurodevelopmental endpoints in children at blood-Pb levels as low as 5 to 10µg/dL. However, the shape of the concentration response curve has not been as extensively examined in these studies; thus, there is still some question as to whether, for endpoints other than IQ, larger effects per incremental dose occur at blood Pb levels <10µg/dL.

3.6.2.2 Cardiovascular outcomes

Epidemiological studies have consistently demonstrated associations between lead exposure and enhanced risk of deleterious cardiovascular outcomes, including increased blood pressure and incidence of hypertension (USEPA, 2006). A meta-analysis of numerous studies estimates that a doubling of blood-lead level (e.g. from 5 to 10µg/dL) is associated with ~1.0mm Hg increase in systolic blood pressure and ~0.6mm Hg increase in diastolic pressure (Nawrot *et al*., 2002). Experimental toxicology studies have confirmed lead effects on cardiovascular functions. Most have shown that exposures creating blood-lead levels of ~20 to 30µg/dL for long periods result in arterial hypertension that persists long after cessation of lead exposure in genetically normal animals.

A number of large population studies in Europe and the United States have reported associations between lead dose and indicators of renal function impairment. Muntner *et al*. (2003) analysed associations between blood lead and renal outcomes in 15,211 adult subjects enrolled in the third National Health and Nutrition Examination study, conducted from 1988 through 1994. Elevated serum creatinine and glomerular filtration rate (GFR) were used as indicators of renal function impairment. Mean blood lead levels were 4.21µg/dL in the 4,813 hypertensives and 3.30 µg/dL in normotensives, (Muntner *et al*. 2003). In a European study of 820 women (age 53 to 64 years) in Sweden, significant negative associations were observed between blood lead and both GFR and creatinine clearance, (Akesson *et al*. 2005). Mean blood lead was only 2.2µg/dL and the association was apparent over the entire dose range.

3.6.3 Toxicological Studies

The results of toxicological studies have found that exposure to Pb is associated with:

- effects on neurobehavioral development and other indicators of nervous system effects
- cardiovascular effects
- heme synthesis effects
- renal effects
- immune system functions
- effects on calcium and vitamin D metabolism
- inter-relationships to bone and teeth formation and demineralization
- effects on reproduction and other neuroendocrine effects
- genotoxicity and carcinogenic effects.

The USEPA (2006) identified that there is little if any evidence from experimental animal studies that allow for any clear delineation at this time of a threshold for neurotoxic effects of Pb.

Neurobehavioral changes have been reported in rodent studies at blood-Pb levels of ~10µg/dL, whereas neurochemical and neurophysiological changes have been reported at blood Pb levels of ~15µg/dL. However, these levels do not necessarily indicate a threshold for such effects but, rather, may only reflect the levels of exposure that have been studied to date.

Lead appears to exhibit a curvilinear, or U-shaped, dose-effect relationship for a number of toxicological endpoints. This effect is not unique to Pb, but occurs with other toxicants (e.g. mercury chloride, chlordane, toluene, and chlorpyrifos) as well, as reviewed by Calabrese

(2005). In the case of Pb, this nonlinear dose-effect relationship occurs in the pattern of glutamate release in the capacity for long term potentiation (LTP), and in conditioned operant responses. Davis and Svendsgaard (1990) reviewed U-shaped dose-response curves and their implications for Pb risk assessment. An important implication is the uncertainty created in identification of thresholds and "no-observed-effect-levels" (NOELS). As a nonlinear relationship is observed between IQ and low blood Pb levels in humans, as well as in new toxicological studies wherein neurotransmitter release and LTP show this same relationship, it is plausible that these nonlinear cognitive outcomes may be due, in part, to nonlinear mechanisms underlying these observed Pb neurotoxic effects (USEPA, 2006).

Studies of immune system effects of lead have been carried out in a range of human and animal trials. These effects are seen in macrophages and T lymphocytes, leading to reduced cell-mediated immunity, increased risk of autoimmunity and tissue inflammation. Epidemiological studies with children have consistently found significant associations between increasing blood lead level and increasing serum IgE levels (Karmaus *et al*., 2005), (Lutz *et al*., 1999), (Sun *et al*., 2003). These effects were evident at blood lead values <10 µg/dL. Heo *et al*. (2004) reported similar associations in adults and animal data has supported this relationship (Chen *et al*. 1999b, Snyder *et al*. 2000).

Findings from numerous experimental studies of rats and of nonhuman primates parallel the observed human neurocognitive deficits and the processes responsible for them. Learning and other higher order cognitive processes show the greatest similarities in Pb-induced deficits between humans and experimental animals. Deficits in cognition are due to the combined and overlapping effects of Pb-induced perseveration, inability to inhibit responding, inability to adapt to changing behavioural requirements, aversion to delays, and distractibility. Higher level neurocognitive functions are affected in both animals and humans at very low exposure levels (<10µg/dL), more so than simple cognitive functions. For example, the discrimination reversal paradigm is a more sensitive indicator of Pb-induced learning impairment than simple discrimination. Many studies suggest that most Pb-induced cognitive deficits are very persistent and that animals remain vulnerable to the effect of Pb throughout development. Some studies, however, suggest that environmental enrichment during early development may confer some offsetting protection against Pb-induced cognitive effects or that other factors (e.g., short-lived exposure duration/low concentration) may, at times, induce detectable but transient cognitive deficits. Also, more evidence is emerging that substantiates Pb-induced attentional deficits, which may contribute to persisting cognitive dysfunction, poorer academic performance, and/or maladaptive anti-social behaviour patterns (e.g. delinquency).

Other behavioural endpoints (e.g. social behaviour, aggression, and locomotor activity) evaluated in animal studies in relation to Pb exposure did not clearly indicate Pb-induced impairments. This may be due to the lack of effect with low-level Pb exposure or to variables (e.g. nutrition, age, gender, and strain) possibly not well controlled for experimentally.

The majority of evidence of the haematological effects of lead is well known and has been covered in detail in previous reviews (USEPA, 1996, Addendum).

3.6.4 Key studies, health outcomes, susceptible groups identified

Several factors have emerged as likely affecting the relative likelihood that humans or laboratory animals may experience Pb-induced neurotoxic effects under particular Pb exposure conditions. Among the more important factors identified thus far are:

- age
- gene-environment interactions
- gender
- socio-economic status.

Identifying discrete periods of development when the foetus or child is particularly susceptible to Pb's effects on neurodevelopment is difficult as (1) age strongly predicts the period of peak exposure (around 18–27 months when there is maximum hand-to-mouth activity), making it difficult to distinguish whether greater neurotoxic effects resulted from increased exposure or enhanced susceptibility at a particular age; and (2) despite changes in actual blood Pb levels, children tend to maintain their relative rank order with regard to neurodevelopment indicators through time, limiting the ability to examine critical periods of development.

Several prospective studies of children with both high and low Pb exposures found concurrent or lifetime average blood-Pb levels to be more strongly associated than other earlier blood-Pb measures with school age IQ and other measures of neurodevelopment (Canfield *et al*., 2003a; Dietrich *et al*., 1993a,b; Tong *et al*., 1996; Wasserman *et al*., 2000b). Using data from the Treatment of Lead-Exposed Children (TLC) study, Chen *et al*. (2005) examined whether cross sectional associations observed in school age children 84–90 months of age represented residual effects from 2 years of age or "new" effects emerging among these children. Concurrent blood- Pb concentration always had the strongest association with IQ. The strength of the cross sectional associations increased over time, despite lower blood-Pb concentrations in older children. Adjustment for prior IQ did not fundamentally change the strength of the association with concurrent blood-Pb level. These results suggest that Pb exposure continues to be toxic to children as they reach school age, but does not support an interpretation that all of the damage occurred by the time the child reaches 2 to 3 years of age. Examination of the toxicological evidence may provide additional evidence, given the difficulties involved in assessing any periods of particularly increased susceptibility to Pb neurodevelopmental health effects in the epidemiological setting.

Most surveys find that boys have higher blood-Pb levels than girls yet the data are less clear with regard to gender-related differences in Pb-associated neurodevelopmental effects. A greater male vulnerability was seen in the Cincinnati Lead Study at various assessments from birth to adolescence. Also, data from a cross-sectional study in England showed more pronounced Pb-IQ deficit associations for boys at 6 years of age. However, in a study of 764 children in Taiwan, the relationship between Pb exposure and IQ scores was much stronger in girls. In the Port Pirie cohort study, Pb effects on cognition were significantly stronger in girls at ages 2, 4, 7, and 11–13 years.

Epidemiological studies have shown that Pb exposure is typically higher among low socioeconomic status (SES) children compared to other U.S. children. Chronic stress and consequent increased levels of glucocorticoids are also associated with low SES. Cory-Slechta *et al*. (2004) have pointed out that both elevated glucocorticoids and Pb can cause similar behavioural changes and that both impact the mesocorticolimbic systems of the brain. The USEPA (2006) concluded that their data indicate a potential mechanism whereby Pb exposure enhances susceptibility to cognitive deficits and disease state.

The most recent review conducted by WHO of the air quality guideline for lead was completed in 2000. WHO (2000) identified that the relationship between air lead exposure

and blood lead has been shown to exhibit downward curvilinearity if the range of exposures is sufficiently large. At lower levels of exposure, the deviation from linearity is negligible and linear models of the relationship between intake and blood lead are satisfactory approximations. The level of lead in blood was considered to be the best available indicator of current and recent past environmental exposure, and may also be a reasonably good indicator of lead body burden with stable exposures. Biological effects of lead will, therefore, be related to blood lead as an indicator of internal exposure.

The WHO (2000) identified a number of adverse health effects in adults associated with Pb exposures including reductions in nerve conduction velocity in lead workers at blood levels as low as 30µg/dL.

A range of health effects in children were also identified by WHO. Reduced haemoglobin levels have been found at concentrations in blood of around 40µg/dL.

Central nervous system effects, as assessed by neurobehavioural endpoints, appear to occur at levels below 20µg/dL. Consistent effects have been reported for global measures of cognitive functioning, such as the psychometric IQ, to be associated with blood lead levels of 10–15µg/dL. WHO also identified some epidemiological studies that have indicated effects at blood lead levels below 10µg/dL.

3.6.5 Blood Lead/Air Lead Slope

In 2000 the Office for Environmental Health Hazard Assessment (OEHHA) reviewed the existing air quality standards for lead and concluded that exposure to airborne lead concentrations at the existing Californian standard of 1.5µg/m^3 (30-day average) would not be protective of the health of children and infants.

At this blood lead level, OEHHA determined that there is consistent evidence from several well-conducted prospective cohort studies that demonstrate an association between blood lead and several adverse neurological outcomes in children, including decreases in IQ. These findings are consistent with those of the USEPA (2006) that lead exposure is associated with neurological effects in children and infants, resulting in diminished measures of intelligence such as IQ, short-term memory loss, reading and spelling underachievement, impairment of visual motor functioning, disruptive classroom behaviour, and impaired reaction time (NRC, 1993). These findings are based on both cross-sectional and prospective studies of human populations.

OEHHA estimated that increases in airborne lead concentrations can result in an increase in blood lead levels in children at an estimated rate of 4.2µg/dL per µg/m^3, after all air-related exposure pathways are included and a steady state has been reached. Reasonable lower and upper bounds for the slope are 3.3 and 5.2, based on the range of geometric means. Although the studies included in their meta-analysis include many different age groups, they concluded that applying the results to the younger children appears reasonable. They assumed that the slope is linear near current ambient air lead concentrations and blood lead levels so that calculations for varied exposures near these levels can be made using the aggregate slope factor.

The WHO guideline for lead in air is based on a critical blood lead concentration of 10µg/dL blood (WHO 2000). Based on a review of experimental and epidemiological studies, the WHO estimated that 1µg/m^3 of lead in air would contribute directly to blood lead in the

range of 1.9µg/dL for children and 1.6µg/dL for adults (WHO 2000). Other research suggested that the total impact of lead in air on blood lead levels (taking into account direct inhalation and indirect uptake through ingesting lead deposited on soil and dust) was in the range of 3–5µg/dL per 1µg/m^3 of lead in air (World Health Organization, 1995).

3.6.6 New studies since international reviews

The Curtin report (Curtin University, 2008) identified a number of studies that have been conducted in recent years. A systematic review of lead exposure and cardiovascular disease through to August 2006, found that the evidence is sufficient to infer a causal relationship of lead exposure with hypertension in adults (Navas-Acien *et al*. 2007). Clinical cardiovascular outcomes such as ischaemic heart disease and stroke were also significantly associated with lead. In an analysis of all-cause and cause-specific mortality from the Third National Health and Nutrition Examination, mean blood lead levels in study participants was 2.58µg/dL (Menke *et al*. 2006). After multivariate adjustment, the hazard ratios (95% CI) for comparisons of participants in the highest tertile of blood lead (≥3.62µg/dL) with those in the lowest tertile (<1.94µg/dL) were 1.25 for all-cause mortality and 1.55 for cardiovascular mortality. Blood lead level was significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels >2µg/dL.

A systematic review of lead exposure and cognitive function in adults identified a number of new adverse effects of cumulative lead exposure (Shih *et al*. 2007). The review concluded that there is sufficient evidence for a causal association between lead and decrements in cognitive function in adults, and that these effects have been observed in populations with mean blood lead levels within the current air quality standards.

With regard to its effect on children, numerous studies demonstrate that even below blood lead concentrations of 10µg/dL there is an inverse relationship with intelligence (Ronchetti *et al*. 2006). Other studies have demonstrated links between behaviour and blood lead, including increased odds of high blood lead levels in youths convicted with delinquent behaviour (Chen *et al*. 2007a, Needleman *et al*. 2002).

3.6.7 Australian studies

Many of the early studies, and most influential studies, on the health effects of lead have been conducted in the lead smelter town of Port Pirie. These studies have shown consistent associations between blood lead levels and decreases in IQ in children. The results of these studies have been reviewed by the USEPA and OEHHA and considered in the development of the existing NEPM standard for lead. More recent Australian studies are summarised below.

In late 2006, the seaside community in Esperance, Western Australia, was alerted to thousands of native bird species dying in and around the town, which was subsequently found to be from lead poisoning. The source of the lead was thought to be from the handling of Pb carbonate concentrate from the Magellan mine through the port of Esperance. Shipping of lead carbonate through the port began in July 2005, and this raised concern in the community about the possible impact of this process on the community health. In consequence, Gulson *et al*, 2009 designed a study to evaluate the source of Pb in blood of a random sample of the community using Pb isotope ratios. The cohort comprised 49 children (48 <5 years of age) along with 18 adults (>20 years of age) with a bias toward higher blood lead levels to facilitate source identification.

The mean blood lead level of the children was 7.5µg/dL (range, 1.5–25.7µg/dL; n = 49; geometric mean, 6.6µg/dL), with four children whose blood lead was >12µg/dL. The isotopic data for blood samples lay around two distinct arrays. The blood of all children analysed for Pb isotopes contained a contribution of Pb from the Magellan mine, which for young children ranged from 27% up to 93% (mean, 64%; median, 71%). Subtraction of the ore component gave a mean background blood lead of 2.3µg/dL. Several children whose blood lead was >9 µg/dL and most of the older subjects have complex sources of Pb. Isotopic data and mineralogic and particle size analyses indicate that, apart from the recognized pathway of Pb exposure by hand-to-mouth activity in children, the inhalation pathway could have been a significant contributor to blood lead for some of the very young children and in some parents.

High precision lead isotope ratios in blood from 58 children aged 1-11 years from the Broken Hill lead mining community have been measured to determine the source and pathways of lead in their blood (Gulson *et al*, 1996). Sources of lead are from the Pb-Zn-Ag ore body, from paint and from petrol. Thirty-five of the 58 children (60%) had blood leads greater than or equal to 15 µg/dL compared with a 'background' level of approximately 6 µg/dL, estimated from adult females who were generally mothers of the children. Six of 17 children aged 7 years or older, had blood lead levels greater than or equal to 15 µg/dL. Even though the ore body lead is the major contributor to blood lead levels in Broken Hill children, of the 35 children whose blood lead is greater than or equal to 15µg/dL, 12 (34%) were found to have approximately 50% or more of their blood lead derived from sources such as paint and petrol or both by isotopic identification. The identification of elevated blood lead in older children was considered a concern, especially for females, as there is potential for release of endogenous lead during pregnancy and lactation.

A further study by Gulson *et al*, 2004, compared high-precision lead isotopic ratios in deciduous teeth and environmental samples to evaluate sources of lead in 10 children from six houses in a primary zinc-lead smelter community at North Lake Macquarie, New South Wales, Australia. For most children, only a small contribution to tooth lead can be attributed to petrol and paint sources. Comparison of isotopic ratios of tooth lead levels with those from vacuum cleaner dust, dust-fall accumulation, surface wipes, ceiling (attic) dust, and an estimation of the smelter emissions indicates that from approximately 55 to 100% of lead could be derived from the smelter.

3.6.8 NHMRC review

In June 2009 the NHMRC reviewed the evidence on the adverse health effects of lead to determine the blood lead levels to be achieved by the Australian population. After considering the evidence for health effects the NHMRC retained the target blood lead level of 10µg/dL, which is the basis for the current lead standard in the AAQ NEPM.

3.6.9 Findings of the review of the lead health evidence

Lead differs from other criteria air pollutants in that it is both persistent in the environment and has multiple exposure pathways whereby air borne dust exposure can be through air, water and soil.

The current NEPM and WHO annual air quality guidelines for lead are 0.5µg/m^3. The USEPA has proposed an action to revise its current lead standard of 1.5µg/m^3, to within the range of 0.10µg/m^3 to 0.30µg/m^3 (USNARA, 2008).

Blood lead levels are the key biomarker of lead exposure. Children remain the group most susceptible to adverse health effects of lead. Evidence has emerged for neurological health effects at blood lead levels less than 10µg/dL, with some studies reporting adverse effects as low as 2µg/dL. Effects measured include lowering of IQ and associations with delinquency. Evidence has also increased for adverse neurological health effects in adults.

Adverse effects on the immune function of children have been demonstrated by epidemiological studies at levels below 10µg/dL. This finding has been supported by animal studies.

Strong evidence exists for a causal relationship between lead and hypertension in adults at blood lead levels less than 10µg/dL. Some evidence exists for an association between lead and cardiovascular morbidity and mortality, but results are inconclusive at this stage.

Renal function impairment in adults, measured as elevated serum creatinine and glomerular filtration rate (GFR) has been reported at blood lead levels between 2 and 10µg/dL in studies with adults in Europe and America.

3.6.9.1 Implications of the health evidence for the lead NEPM standard

The evidence from recent international studies and reviews has identified a range of adverse health effects of lead at blood lead levels of between 2 and 10µg/dL.

The NHMRC state that the recently reconfirmed blood level of 10µg/dL is not intended to be interpreted as either a "safe" level of exposure or a "level of concern" (NHMRC, 2009). In light of the fact that current NEPM air quality guidelines are based on a critical blood lead level of 10µg/dL, adverse health effects may occur at levels below current guidelines. Taking into account the multiple exposure pathways of lead in air, an upper range estimate is that 0.5µg/m^3 of lead in air could contribute 2.5µg/dL to blood lead levels.

The current NEPM standard is based on 10µg/dL blood lead level.

3.7 Particles

3.7.1 Introduction

In recent years the health effects of particles linked to ambient exposures have been well studied and reviewed by international agencies (USEPA, 2004, 2009; WHO, 2006; OEHHA, 2000). A comprehensive evaluation of the evidence relating to particles in ambient air and impacts on health is contained in *AAQ NEPM Health Reviews 2009*.

Unlike the other criteria pollutants, particles are a broad class of chemically and physically diverse substances. They exist as discrete particles spanning several orders of magnitude in size, 0.005 to 100µm. They are emitted from a wide range of sources including natural sources such as dusts and pollens. The biological effects of particles are determined by

- the physical and chemical nature of the particles

- the physics of deposition and distribution in the respiratory tract
- the physiological events that occur in response to the presence of the particle.

In recent years a significant amount of research has focussed on the health effects of particles and an increasing body of literature reports associations between particles and adverse health effects. Effects have been found for both PM_{10} and $PM_{2.5}$ and to a lesser extent, ultrafine particles (UFPs). Most information comes from population-based epidemiological studies that find increases in daily mortality as well as morbidity outcomes such as increases in hospital admissions and emergency room attendances, and exacerbation of asthma associated with daily changes in ambient particle levels. There has been an increasing focus on the link between exposure to particles and cardiovascular outcomes. In addition to studies on the various size metrics for particles, recent research has also investigated the role of particle composition in the observed health effects.

The evidence on the health effects of particles comes from several major lines of scientific investigation: characterisation of inhaled particles; consideration of the deposition and clearance of particles in the respiratory tract and the doses delivered to the upper and lower airway and the alveoli; animal and cellular studies of toxicity; studies involving inhalation of particles by human volunteers; and population-based epidemiological studies. The findings of these different lines of investigation are complementary and each has well-identified strengths and limitations. While the findings of epidemiological studies have been given the greatest weight in setting standards for airborne particles, studies on human volunteers (clinical studies) can provide information on exposure–response relationships for acute, transient effects in healthy and potentially susceptible individuals. Studies of this design, involving both healthy persons and adults with chronic diseases, have been carried out using exposure to concentrated ambient particles.

3.7.2 Short-term effects

Most of the evidence of an association between short-term exposure to particles and adverse health outcomes comes from time-series studies looking at daily increases in mortality and hospital admissions and emergency room attendances linked to ambient particle concentrations. In addition the results of panel studies and controlled exposure studies add further evidence for the association between short-term exposure to particles and adverse health effects. The results of recent reviews and studies are summarised below.

3.7.2.1 Mortality

The association between exposure to both PM_{10} and $PM_{2.5}$ and increases in daily mortality have been the subject of extensive research. The results of these studies show that particles are linked to increases in all cause mortality and well as cause specific mortality such cardiovascular and respiratory causes. There is also some evidence that exposure to thoracic particles, $PM_{10\text{-}2.5,}$ is also linked with increases in daily mortality.

The epidemiological literature indicates consistent positive associations between short-term exposure to PM_{10} and all-cause mortality. The results of multicity studies report an approximate 0.12–0.81% increase in all-cause mortality per 10µg/m^3 increase in PM_{10} with 24-h average PM_{10} concentrations ranging from 13 to 53.2µg/m^3. Consistent positive associations have also been found between PM_{10} and respiratory and cardiovascular-related mortality. Studies conducted in Australia have found similar results with a 0.2% (-0.8–1.2%) increase in all-cause mortality per 10µg/m^3 increase in 24-hour average PM_{10} (Simpson *et al*.,

2005a). Heterogeneity in PM_{10} mortality risk estimates is observed between cities and studies, including Australian studies, which could be attributed to the lag, averaging time, number of cities and/or co-pollutants included in the regression models. An evaluation of the lag structures used in the multicity studies found that the greatest effects were observed using the previous day's PM_{10} concentration (lag 1) or the average of the same day's and previous day's concentrations (lag 0–1). In addition, the use of a distributed lag model resulted in slightly larger (by ~30%) estimates compared to single-day lags. In the US studies regional heterogeneity and seasonal patterns in PM_{10} risk estimates were also observed, with the greatest effects occurring in the Eastern U.S. and during the summer and transition seasons, spring and autumn, respectively. Similar heterogeneity and seasonality has been observed in Australian studies (Simpson *et al*., 2005a and b); Barnett *et al*., 2005; 2006) An examination of potential confounders (i.e., temperature and co-pollutants) using different study designs (i.e., time series and case crossover) observed that neither is likely to account for differences in PM_{10}-mortality risk estimates between studies. However, one Canadian-based multicity study did observe a reduction in the PM_{10} mortality risk estimate upon the inclusion of NO_2 in the model. The USEPA (2009) found that the consistent evidence observed across epidemiological studies is sufficient to conclude that a causal relationship is likely to exist between short-term exposure to ambient concentrations of PM_{10} and mortality. WHO (2006) and Cal EPA (2001) came to similar conclusions.

In recent years there has been a significant increase in studies showing associations between particles and cardiovascular effects. Epidemiological studies that examined the association between PM_{10}, $PM_{2.5}$ and mortality have provided strong evidence for particle-related cardiovascular effects. Multicity studies have found consistent, positive associations between short-term exposure to $PM_{2.5}$ and cardiovascular mortality ranging from 0.47 to 0.85% at mean 24-h avg $PM_{2.5}$ concentrations above 13µg/m^3. These associations were reported at short lags (0-1 days) Although examinations of potential confounders of the $PM_{2.5}$-cardiovascular mortality relationship are limited, the observed associations are supported by PM_{10}-mortality studies, which found that particle risk estimates remained robust to the inclusion of co-pollutants in models. Although the overall effect estimates reported in the multicity studies are consistently positive, it should be noted that a large degree of variability exists between cities when examining city-specific effect estimates potentially due to differences between cities and regional differences in $PM_{2.5}$ composition.

Burnett *et al*. (2004) examined the association between mortality and various air pollutants in 12 Canadian cities, and reported that the most consistent association was found for NO_2. For this analysis, particles were measured every 6th -day for the majority of the study period, and the PM_{10} concentrations used in the study represent the sum of the $PM_{2.5}$ and $PM_{10\text{-}2.5}$, which were directly measured by dichotomous samplers. The authors found that the simultaneous inclusion of NO_2 and PM_{10} in a model, on those days with particle data, greatly reduced the PM_{10} association with non-accidental mortality, from 0.47% (95% CI: 0.04-0.89) to 0.07% (95% CI: -0.44 to 0.58) per 10µg/m^3 increase. The PM_{10} risk estimates in the Canadian data appear to be more sensitive to NO_2 than those estimates reported in U.S. studies.

The association between PM_{10} and mortality in Europe has been extensively studies (Katsouyanni *et al*. 2003), which presented results from the Air Pollution and Health: a European Approach (APHEA2) study, a multicity study that examined PM_{10} effects on total mortality in 29 European cities. In a later APHEA study Analitis *et al*. (2006) published a report on effect estimates for cardiovascular and respiratory deaths also based on the 29 European cities, within the APHEA2 study. The results of this study found for the average

of 0- and 1-day lags, PM_{10} risk estimates per 10µg/m^3 of 0.76% (95% CI: 0.47–1.05) for cardiovascular deaths and 0.71% (95% CI: 0.22–1.20) for respiratory deaths in random effects models.

The APHENA study (Samoli *et al*., 2008) was a collaborative effort by the APHEA, NMMAPS, and the Canadian multicity study investigators to evaluate the coherence of PM_{10} mortality risk estimates across locations and possible effect modifiers of the particle-mortality relationship using a common protocol. The results of the APHENA study showed that generally, the risk estimates from Europe and the U.S. were similar, but those from Canada were substantially higher. For example, the percent excess risks per 10µg/m^3 increase in PM_{10} for all ages using 8df/yr and penalized splines were 0.84% (0.30, 1.40), 0.33% (0.22, 0.44), and 0.29% (0.18, 0.40) for the Canadian, European, and U.S. data, respectively. Note that the risk estimate for the 90 U.S. cities is slightly larger than that reported in the original NMMAPS study (0.21%, using natural splines, and more temperature variables). In the all ages model, the average of lag days 0 and 1, and the distributed lag model with lags 0, 1, and 2 did not result in larger risk estimates compared to those for a 1 day lag. In co-pollutant models, PM_{10} risk estimates did not change when controlling for O_3. The Canadian data appear less sensitive to the extent of temporal smoothing or smoothing methods. When stratifying by age the risk estimates for the older age group (age ≥ 75) were consistently larger than those for the younger age group (age <75) (e.g., 0.47% vs. 0.12% for the U.S. data) for all the three data sets. Although the study did not quantitatively present the results from the effect modification analyses, some evidence of effect modification across the study regions was observed. The investigators reported that, in the European data, higher levels of NO_2 and a larger NO_2/PM_{10} ratio were associated with greater PM_{10} risk estimates, and that while this pattern was also present in the U.S. data, it was less pronounced. Additionally, in the U.S. data, smaller PM_{10} risk estimates were observed among older adults in cities with higher O_3 levels. Effect modification by temperature was also observed, but only in the European data. It is important to note that the results observed in the Canadian studies are comparable to those observed in the Australian studies (Simpson *et al*., 2005a).

A study conducted in four Australian cities (Brisbane, Melbourne, Perth and Sydney), found significant associations between particles and all cause mortality. Meta-analyses carried out for three cities yielded estimates for the increase in the daily total number of deaths of 0.2% (-0.8% to 1.2%) for a 10µg/m^3 increase in PM_{10} concentration, and 0.9% (-0.7% to 2.5%) for a 10µg/m^3 increase in $PM_{2.5}$ concentration.

A study conducted in Melbourne found significant positive associations between the particle measures considered and all cause and respiratory mortality in the warm season (November-March). A 10µg/m^3 increase in 24-h $PM_{2.5}$ in the warm season was associated with a 0.38% (95% CI, 0.06–0.70%) increase in risk of death for all cause mortality and a 1.18% (95% CI, 0.05–2.32%) increase in risk for respiratory mortality. For PM_{10}, a 10µg/m^3 was associated with an increased risk of 0.18% (95% CI, 0.03–0.33%) for all cause mortality and 0.59% (95% CI, 0.06–1.13%) for respiratory mortality. Significant associations were also found in the 65+ age group in the warm season (Simpson *et al*. 2000).

A study of ambient levels of air pollution in Melbourne and daily mortality due to all causes, respiratory and cardiovascular disease found that after controlling for the effects of weather and other confounding factors, air pollution in Melbourne is associated with increases in daily mortality. Associations were found between mortality and O_3, NO_2, CO and $PM_{2.5}$ with the strongest and most robust relationships being observed for ozone and

nitrogen dioxide with smaller increases in mortality being noted with $PM_{2.5}$ (EPA Victoria, 2000).

An evaluation of the epidemiological literature indicates consistent positive associations between short-term exposure to $PM_{2.5}$ and all-cause, cardiovascular- and respiratory-related mortality. The evaluation of multicity studies found that risk estimates for all-cause (non-accidental) mortality ranged from 0.29% to 1.21% per 10µg/m^3 increase in 24-hour average $PM_{2.5}$ at lags of 1 and 0–1 days. These consistent effects were observed in study locations with mean 24-h average $PM_{2.5}$ concentrations as low as 13µg/m^3. Cardiovascular-related mortality risk estimates were found to be similar to those for all-cause mortality whereas, the risk estimates for respiratory-related mortality were consistently larger: 1.01–2.2% using the same lag periods and averaging indices. Results of studies in the US showed regional and seasonal patterns in $PM_{2.5}$ risk estimates with the greatest effect estimates occurring in the eastern U.S. and during the spring. Of the studies evaluated by the USEPA in their most recent review (USEPA, 2009) no U.S.-based multicity studies conducted a detailed analysis of the potential confounding of $PM_{2.5}$ risk estimates by gaseous pollutants. However Burnett *et al*. (2004) found mixed results, similar to those observed for PM_{10}, with possible confounding by NO_2 when analysing gaseous pollutants in a multicity Canadian-based study. An examination of effect modifiers (e.g., demographic and socioeconomic factors), specifically air conditioning use as an indicator for decreased pollutant penetration indoors, has suggested that $PM_{2.5}$ risk estimates increase as the percent of the population with access to air conditioning decreases (USEPA, 2009). Collectively, the USEPA (2009) concluded that the epidemiological literature provides evidence that a causal relationship is likely to exist between short-term exposures to $PM_{2.5}$ and mortality. This finding is supported by WHO (2006) and Cal EPA (2001).

Franklin *et al*. (2007) analysed 27 cities across the U.S. that had $PM_{2.5}$ monitoring and daily mortality data for at least 2 yr of a 6-yr period 1997 to 2002. The mortality data up to year 2000 were obtained from the National Centre for Health Statistics, while the 2001–2002 data were obtained from six states (California, Michigan, Minnesota, Pennsylvania, Texas, and Washington), resulting in 12 out of the 27 cities having data up to 2002. The start year for each city included in the study was set at 1999, except for Milwaukee, Wisconsin (1997) and Boston, Massachusetts (1998), as $PM_{2.5}$ data was available in these two cities. In the case-crossover analysis in each city, control days for each death were chosen to be every third day within the same month and year that death occurred in order to reduce auto-correlation. The first stage regression examined the interaction of effects with age and gender, while the second stage random effects model combined city-specific $PM_{2.5}$ risk estimates and examined possible effect modifiers using city-specific characteristics (e.g., prevalence of central air conditioning and geographic region). For all of the mortality categories, the estimates for lag 1-day showed the largest estimates. The combined estimates at lag 1 day were: 1.2% (CI: 0.29–2.1), 0.94% (CI: -0.14 to 2.0), 1.8% (CI: 0.20–3.4), and 1.0% (CI: 0.02–2.0) for all-cause, cardiovascular, respiratory, and stroke deaths, respectively, per 10µg/m^3 increase in 24-hour average $PM_{2.5}$.

Zanobetti and Schwartz (2009) analysed $PM_{2.5}$ associations with all-cause, cardiovascular disease, myocardial infarction, stroke, and respiratory mortality for the years 1999–2005. The overall combined excess risk estimates were: 0.98% (0.75, 1.22) for all-cause; 0.85% (0.46, 1.24) for cardiovascular disease, 1.18% (0.48, 1.89) for myocardial infarction; 1.78% (0.96, 2.62) for stroke, and 1.68% (1.04, 2.33) for respiratory mortality for a 10µg/m^3 increase in $PM_{2.5}$ at lag 0–1. When the risk estimates were combined by season, the spring estimates were the largest for all-cause and for all of the cause-specific mortality outcomes examined.

The risk estimate for all-cause mortality for the spring was 2.57% (1.96–3.19) with the estimates for the other seasons ranging from 0.25% to 0.95%. When examining cities that had both $PM_{2.5}$ and $PM_{10-2.5}$ data (i.e., 47 cities), the addition of $PM_{10-2.5}$ in the model did not alter the $PM_{2.5}$ estimates substantially, only decreasing slightly from 0.94% in a single pollutant model to 0.77% in a co-pollutant model with $PM_{10-2.5}$,. When the risk estimates were combined by climatic regions, the estimated $PM_{2.5}$ risk for all-cause mortality were similar (all above 1% per 10µg/m^3 increase) for all the regions except for the "Mediterranean" region (0.5%) which include cities in California, Oregon and Washington, though the estimates in that region were significantly heterogeneous.

Studies looking at $PM_{10-2.5}$ and cardiovascular mortality have also found associations with this size fraction (USEPA, 2009). Zanobetti and Schwartz (2009) examined $PM_{10-2.5}$ mortality associations in 47 U.S. cities and found evidence for cardiovascular mortality effects (0.32% [95% CI: 0.00–0.64] per 10 µg/m^3 at lag 0–1) similar to those reported for all-cause (non-accidental) mortality (0.46% [95% CI: 0.21–0.67] per 10µg/m^3). Seasonal (i.e., larger in spring and summer) and regional differences in $PM_{10-2.5}$ cardiovascular mortality risk estimates were observed in this study. The study found a significant association between the computed $PM_{10-2.5}$ and all-cause, cardiovascular disease, stroke, and respiratory mortality. The combined estimate for the 47 cities using the average of 0- and 1-day lag $PM_{10-2.5}$ for all-cause mortality was 0.46% (95% CI: 0.21–0.71) per 10µg/m^3 increase with the estimate obtained using the distributed lag model being smaller (0.31% [95% CI: 0.00–0.63]). The seasonal analysis showed larger risk estimates in the spring for all-cause (1.01%) and respiratory mortality (2.56%), however, for cardiovascular mortality, the estimates for spring (0.95%) and summer (1.00%) were comparable. Zanobetti and Schwartz (2009) also found an association between $PM_{10-2.5}$ and respiratory mortality (1.16% [95% CI: 0.43, 1.89] per 10µg/m^3 at lag 0–1), with effect estimates somewhat larger than those reported for all-cause (non-accidental) mortality (0.46% [95% CI: 0.21, 0.671] per 10µg/m^3). In addition, Zanobetti and Schwartz (2009) reported seasonal (i.e., larger in spring) and regional differences in $PM_{10-2.5}$ respiratory mortality risk estimates.

A few single-city studies evaluated also reported associations, albeit somewhat larger than the multicity study, between $PM_{10-2.5}$ and cardiovascular mortality in Phoenix, Arizona (Wilson *et al*., 2007) (3.4-6.6% at lag 1) and Vancouver, Canada (Villeneuve *et al*., 2003) (5.4% at lag 0). The difference in the $PM_{10-2.5}$ risk estimates observed between the multi- and single-city studies could be due to a variety of factors including differences between cities and compositional differences in $PM_{10-2.5}$ across regions (USEPA, 2009).

Single-city studies conducted in Atlanta, Georgia (Klemm *et al*., 2004) and Vancouver, Canada (Villeneuve *et al*., 2003) reported no associations between short-term exposure to $PM_{10-2.5}$ and respiratory mortality. The difference in the results observed between the multi- and single- city studies could be due to a variety of factors including differences between cities and compositional differences in $PM_{10-2.5}$ across regions. Only a small number of studies have examined potential confounding by gaseous co-pollutants or the influence of model specification on $PM_{10-2.5}$ mortality risk estimates.

A study by Perez *et al*. (2008) investigated the association between Saharan dust events and the effects of $PM_{2.5}$ and $PM_{10-2.5}$ on daily mortality. Changes of effects between Saharan and non-Saharan dust days were assessed using a time-stratified case-crossover design involving 24,850 deaths between March 2003 and December 2004 in Barcelona, Spain. Saharan dust days were identified from back-trajectory and satellite images. Chemical speciation, but not an analysis for microbes or fungi, was conducted approximately once a

week during the study period. On Saharan dust days, mean concentrations were 1.2 times higher for $PM_{2.5}$ (29.9µg/m^3) and 1.1 times higher for $PM_{10\text{-}2.5}$ (16.4µg/m^3) than on non-Saharan dust days. During Saharan dust days (90 days out of 602), the $PM_{10\text{-}2.5}$ risk estimate was 8.4% (95% [CI: 1.5–15.8]) per 10µg/m^3 increase at lag 1 day, compared with 1.4% (95% CI: -0.8% to 3.4%]) during non-Saharan dust days. In contrast, there was not an additional increased risk of daily mortality for $PM_{2.5}$ during Saharan dust days (5.0% [95% CI: 0.5–9.7]) compared with non-Saharan dust days (3.5% [95% CI: 1.6–5.5]). However, differences in chemical composition (i.e., $PM_{2.5}$ was primarily composed of non-mineral carbon and secondary aerosols; whereas $PM_{10\text{-}2.5}$ was dominated by crustal elements) did not explain these observations.

Canadian studies have also shown an association between $PM_{10\text{-}2.5}$ and mortality (Burnett *et al*., 2004; Villeneuve *et al*. 2003). The Burnett study found a 0.65% (CI: -0.10 to 1.4) increase in all cause mortality per 10µg/m^3 increase at lag 1 day. When both NO_2 and $PM_{10\text{-}2.5}$ were included in the regression model, the $PM_{10\text{-}2.5}$ effect estimate was reduced to 0.31% (95% CI: -0.49 to 1.1) per 10µg/m^3 increase in 1-day lag $PM_{10\text{-}2.5}$. These risk estimates are similar to those reported for $PM_{2.5}$, which were also reduced upon the inclusion of NO_2 in the two-pollutant model, but to a greater extent, from 0.60% (95% [CI: -0.03 to 1.2]) to -0.1% (95% [CI: -0.86 to 0.67]). The study by Villeneuve *et al*. (2003) analysed the association between $PM_{2.5}$, $PM_{10\text{-}2.5}$, TSP, PM_{10}, SO_4^{2-}, and gaseous co-pollutants in Vancouver, Canada, using a cohort of approximately 550,000 between 1986 and 1999. In this study $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were directly measured using dichotomous samplers. The authors examined the association of each air pollutant with all-cause, cardiovascular, and respiratory mortality, but only observed significant results for cardiovascular mortality at lag 0 for both $PM_{10\text{-}2.5}$ and $PM_{2.5}$. They found that $PM_{10\text{-}2.5}$ (5.4% [95% CI: 1.1–9.8] per 10µg/m^3), was more strongly associated with cardiovascular mortality than $PM_{2.5}$ (4.8% [95% CI: -1.9 to 12.0] per 10µg/m^3).

Multicity studies that examined the association between $PM_{2.5}$ and respiratory mortality, Franklin *et al*. (2007) and Zanobetti and Schwartz (2009), found consistent, positive associations between short-term exposure to $PM_{2.5}$ and respiratory mortality ranging from 1.67 to 2.20% at lag 0–1 for mean 24-h $PM_{2.5}$ average concentrations above 13µg/m^3. Although examinations of potential confounders of the $PM_{2.5}$-respiratory mortality relationship are limited, the observed associations are supported by PM_{10}-mortality studies, which found that particle risk estimates remained robust to the inclusion of co-pollutants in models. The associations are consistent with those presented by Ostro *et al*. (2006) in a study that examined the $PM_{2.5}$-mortality relationship in 9 California counties (2.2% [95% CI: 0.6–3.9] per 10µg/m^3). An evaluation of studies that examined additional lag structures of associations found smaller respiratory mortality effect estimates when using the average of lag days 1 and 2 (1.01% [95% CI: -0.03 to 2.05] per 10µg/m^3) (Franklin *et al*., 2008), and associations consistent with those observed at lag 0–1 when examining single day lags, specifically lag 1 (1.78% [95% CI: 0.2–3.36]). Although the overall effect estimates reported in the multicity studies evaluated are consistently positive, it should be noted that a large degree of variability exists between cities when examining city-specific effect estimates both in the US and in Australia, potentially due to differences between cities and regional differences in $PM_{2.5}$ composition.

3.7.2.2 Morbidity

The majority of recent evidence for an association between short-term exposure to PM_{10} and cardiovascular health effects is derived from epidemiological studies of hospital admissions and emergency department visits. Although some regional heterogeneity is evident in the

single-city effect estimates, consistent increases in hospital admissions and emergency department visits for cardiovascular diseases, have been observed across studies, with the majority of estimates ranging from 0.5–1.0% per 10μg/m^3 increase in PM_{10}. A detailed examination of specific cardiovascular health outcomes has suggested that ischemic heart disease and chronic heart failure are responsible for the majority of particle-related cardiovascular disease hospital admissions rather than cerebrovascular diseases; however, one large multicity study provides evidence of an association between PM_{10} and ischemic stroke. Overall, the new literature provides consistent evidence for associations between short-term exposure to PM_{10} and increased risk of cardiovascular hospital admissions and emergency department visits in cities with mean 24-h average concentrations ranging from 16.8 to 48μg/m^3.

Recent large studies conducted in the U.S., Europe, and Australia and New Zealand have confirmed these findings for PM_{10}, and have also observed consistent associations between $PM_{2.5}$ and cardiovascular hospitalisations. However, findings from single-city studies have demonstrated regional heterogeneity in effect estimates. It is apparent from these recent studies that the observed increases in cardiovascular hospitalisations are largely due to admissions for ischemic heart disease and congestive heart failure rather than cerebrovascular diseases (such as stroke). Associations have been found for short-term increases in ambient levels of PM_{10} and $PM_{2.5}$ and increased risk of hospitalisation or emergency department visits for ischemic heart diseases. The evidence for an association of cardiovascular disease hospitalisation with $PM_{10-2.5}$ is limited and although the estimates are less precise for $PM_{10-2.5}$, most results from single pollutant models provide evidence of a positive association between $PM_{10-2.5}$ and ischemic heart disease. Peng *et al*. (2008) reported that the association with $PM_{10-2.5}$ was not robust to adjustment for $PM_{2.5}$ and estimates from the other studies are imprecise. Host *et al*. (2008) found that the effect estimates for the association of $PM_{2.5}$ and $PM_{10-2.5}$ with ischemic heart disease were very similar when scaled to the IQR of each metric. The average excess risk among the elderly is in the range of 0.5 to 1.0% per 10μg/m^3 increase in $PM_{2.5}$, although substantial variability by region of the country and season has been demonstrated. The association between particles and hospital admissions for cardiovascular disease and ischemic heart disease appear to be greater in Europe and Australia/New Zealand than in the U.S (USEPA, 2009; WHO, 2006).

A large body of evidence from studies of the effect of $PM_{2.5}$ on hospital admissions and emergency department visits for cardiovascular diseases has shown that associations with $PM_{2.5}$ are consistently positive with the majority of studies reporting increases in hospital admissions or emergency department visits ranging from a 0.5 to 3.4% per 10μg/m^3 increase in $PM_{2.5}$. A large U.S-based multicity study reported excess risks in the range of approximately 0.7% with the largest excess risks in the North East (1.08%) and in the winter (1.49%), providing evidence of regional and seasonal heterogeneity (Bell *et al*., 2008; Dominici *et al*., 2006). Weak or null findings for $PM_{2.5}$ have been observed in two single-city studies both conducted in Washington State (Slaughter *et al*., 2003; Sullivan *et al*., 2007) and may be explained by this heterogeneity. Weak associations were also reported in Atlanta for $PM_{2.5}$ and cardiovascular disease emergency department visits, with $PM_{2.5}$ traffic components being more strongly associated with cardiovascular disease emergency department visits (Tolbert *et al*., 2007). The results of multicity studies conducted outside the U.S. and Canada have shown positive associations with $PM_{2.5}$. Studies of specific cardiovascular disease outcomes indicate that ischemic heart disease and congestive heart failure may be driving the observed associations. Although estimates from studies of cerebrovascular diseases are less precise and consistent, ischemic diseases appear to be more strongly associated with $PM_{2.5}$ compared to hemorrhagic strokes. The available evidence

suggests that these effects occur at very short lags (0-1 days), although effects at longer lags have rarely been evaluated. Overall, the results of these studies provide support for associations between short-term $PM_{2.5}$ exposure and increased risk of cardiovascular hospital admissions in areas with mean concentrations ranging from 7 to 18µg/m^3.

Large studies from Europe and Australia/New Zealand report positive associations between short-term increases in ambient levels of PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ and increased risk of hospital admissions for cardiac disease. The results from small single-city studies are less consistent. The excess risk for cardiac hospital admissions may be somewhat larger than for total cardiovascular hospitalisations. The results of these studies also provide support for an association between short-term increases in ambient levels of PM_{10} and $PM_{2.5}$ and increased risk of hospitalisation for myocardial infarction, but not all studies have found statistically significant associations. Some of the heterogeneity of results is likely explained by regional differences in pollution sources, components, and measurement error. One study of the effect of 2- and 24-h average $PM_{10-2.5}$ concentration on admissions for myocardial infarction produced effect estimates that were positive but imprecise (Peters *et al*., 2001). These results need to be interpreted together with those studies evaluating hospitalisation for ischemic heart disease since myocardial infarctions make up the majority of hospital admissions for ischemic heart diseases.

Relatively few studies have evaluated the effects of $PM_{2.5}$ and $PM_{10-2.5}$ on the risk of hospital admissions and emergency department visits in the context of 2 pollutant models. Generally, results for health effects of both size fractions are similar even after controlling for SO_2 or O_3. However, controlling for NO_2 or CO has yielded conflicting results. Among the large multicity studies, the Atlanta-based SOPHIA study found that the association between $PM_{2.5}$ (total carbon) and risk of cardiovascular emergency department visits was somewhat attenuated in 2-pollutant models controlling for either CO or NO_2 (Tolbert *et al*., 2007). Barnett *et al*. (2006,) found that the associations between $PM_{2.5}$ and cardiac hospital admissions in Australia and New Zealand were attenuated after control for 24-h NO_2, but not after control for CO. A number of studies have also evaluated PM_{10} effects in the context of 2-pollutant models with inconsistent results. The multicity Spanish EMECAS study (Ballester *et al*., 2006) found that the statistically significant positive associations observed between PM_{10} and cardiac hospital admissions were robust to control for other pollutants in 2-pollutant models. Jalaludin *et al*. (2006) found that the effects of PM_{10} as well as $PM_{2.5}$ on cardiovascular emergency department visits in Sydney were attenuated by additional control for either NO_2 or CO. Wellenius *et al*. (2005) found that the PM_{10}-related risk of hospitalisation for congestive heart failure in Allegheny County, Pennsylvania, was attenuated in 2-pollutant models controlling for either CO or NO_2. In contrast, Chang *et al*. (2004) examined hospital admissions for congestive heart failure in Taipei and found attenuation of PM_{10} effects by control for NO_2 or CO, but only during warm days. In Kaohsiung, Taiwan, Tsai *et al*. (2003) found that the association between PM_{10} and hospital admissions for ischemic stroke was not significantly attenuated in 2-pollutant models controlling for either NO_2 or CO.

Only a few studies have attempted to evaluate the effects of one particle size fraction while controlling for another particle size fraction. The large U.S. MCAPS study evaluating the effects of $PM_{10-2.5}$ on cardiovascular hospital admissions lost precision after controlling for $PM_{2.5}$, but did not consider gaseous pollutants (Peng *et al*., 2008). Andersen *et al*. (2008) found that associations between both PM_{10} and $PM_{2.5}$ and hospital admissions for cardiovascular disease in Copenhagen were not attenuated by control for particle number concentration, a measure of ultrafine particles.

Recent animal toxicological studies have shown impacts on the cardiovascular system. An inhalation study in animals found lowered cardiac contractility upon exposure to PM_{10}, while several intratracheal instillation studies found altered vasoreactivity and elevated levels of systemic inflammatory and blood coagulation markers. In addition, several epidemiological studies have observed physiologic alterations in cardiovascular function including: heart rate variability (HRV), systemic markers of inflammation, coagulation, and oxidative stress in cities with mean 24-h average concentrations ranging from 10.5 to 46.1µg/m^3. These findings, along with those reported in the toxicological literature contribute to the biological plausibility of PM_{10}-related cardiovascular effects. Overall, consistent and coherent evidence exists across recent toxicological and epidemiological studies, which supports the conclusion that short-term exposure to PM_{10} is associated with an increased risk of cardiovascular morbidity. Furthermore, findings of altered autonomic function, cardiac contractility, systemic inflammation, coagulation, and vasoreactivity provide biological plausibility that exposure to PM_{10} could lead to more severe effects, including hospital admissions or emergency department visits for ischemic heart disease, congestive heart failure, or ischemic stroke. The USEPA (2009) concluded that collectively, these studies provide sufficient evidence to conclude that a causal relationship is likely to exist between short-term exposure to ambient concentrations of PM_{10} and cardiovascular morbidity.

Recent studies have found consistent associations between $PM_{2.5}$ and hospital admissions and emergency department visits for respiratory disease with effect estimates in the range of ~1–4% per 10µg/m^3 increase in $PM_{2.5}$. These associations have been observed in areas with mean 24-h $PM_{2.5}$ concentrations between 6.1 and 22µg/m^3. Further, recent studies have focused on increasingly specific disease endpoints such as asthma, COPD and respiratory infection. The strongest evidence of an association comes from large multicity studies of COPD, respiratory tract infection and all respiratory diseases among Medicare recipients (65+ years old) (Dominici *et al*., 2006; Bell *et al*., 2008). Studies of children have also found evidence of an effect of $PM_{2.5}$ on hospital admissions for all respiratory diseases, including asthma and respiratory infection. One of the strongest associations observed in the Atlanta-based SOPHIA study was between PM_{10} and paediatric asthma visits; $PM_{2.5}$ makes up a large proportion of PM_{10} in Atlanta (Peel *et al*., 2005); Positive associations between $PM_{2.5}$ (or PM_{10}) and hospital admissions for respiratory infection are supported by animal toxicological studies which add to previous findings of increased susceptibility to infection following exposure to $PM_{2.5}$. These include studies demonstrating reduced clearance of bacteria (Pseudomonas, Listeria) or enhanced pathogenesis of viruses (influenza, RSV) after exposure to diesel exhaust or residual oil fly ash.

The majority of the studies that examined the association between $PM_{2.5}$ and respiratory symptoms and medication use found a consistent increase in asthmatic children (effect estimates ranging from ~1.0–1.3) with less consistent evidence for an association in asthmatic adults in cities with mean 24-h average $PM_{2.5}$ concentrations ranging from 6.1 to 19.2µg/m^3. An evaluation of epidemiological studies that examined specific physiologic alterations in the respiratory health of asthmatic children (i.e., pulmonary function and pulmonary inflammation) found a decrease in forced expiratory volume (FEV1) ranging from 1-3.4% per 10µg/m^3 increase in $PM_{2.5}$; and an increase in eNO ranging from 0.46 to 6.99ppb, respectively. In addition, epidemiological studies that examined the effect of short-term exposure to $PM_{2.5}$ on respiratory hospital admissions and emergency department visits found consistent associations (ranging from ~0 to 5%) for respiratory diseases (e.g. COPD and respiratory infections) among older adults, but less consistent effects were reported for

asthma hospital admissions and emergency department visits. These respiratory hospital admissions and emergency department visit studies were conducted in cities with mean 24-h average $PM_{2.5}$ concentrations ranging from 13.8 to 18.9µg/m^3.

The evidence for $PM_{2.5}$ induced respiratory effects is strengthened by similar associations found for hospital admissions and emergency department visit for PM_{10}, along with the consistent positive associations observed between $PM_{2.5}$ and respiratory mortality in multicity studies. Panel studies also indicate associations with $PM_{2.5}$ and respiratory symptoms, pulmonary function, and pulmonary inflammation among asthmatic children. Controlled human exposure studies in adults demonstrating increased markers of pulmonary inflammation following diesel exhaust and other traffic-related exposures, oxidative responses to diesel exhaust and wood smoke and exacerbations of allergic responses and allergic sensitization following exposure to diesel exhaust particles add further support for these effects. Some controlled human exposure studies have reported small decrements in various measures of pulmonary function following controlled exposures to $PM_{2.5}$. Numerous toxicological studies demonstrating a wide range of responses provide biological plausibility for the associations between $PM_{2.5}$ and respiratory morbidity observed in epidemiological studies. Altered pulmonary function, mild pulmonary inflammation and injury, oxidative responses, Airway hyperresponsiveness in allergic and non-allergic animals, exacerbations of allergic responses and increased susceptibility to infections were observed in a large number of studies involving exposure to concentrated ambient particles, diesel exhaust, other traffic-related particles and wood smoke. The numerous and wide range of respiratory responses observed in both the human clinical and toxicological studies provide biological plausibility for an association between short-term exposure to $PM_{2.5}$ and respiratory morbidity. The USEPA, (2009) concluded that the consistent and coherent results found in the epidemiological, human clinical, and toxicological literature provide sufficient evidence that a causal relationship is likely to exist between short-term exposures to ambient concentrations of $PM_{2.5}$ and respiratory morbidity.

Epidemiological studies that examined the association between short-term exposure to PM_{10} and respiratory morbidity found consistent positive effects in asthmatic children and adults, but no evidence of an association in healthy individuals. The majority of the studies that examined the association between PM_{10} and respiratory symptoms and medication use found an increased risk ranging from ~1.0 to 1.75 for cough, phlegm, difficulty breathing, and bronchodilator use in asthmatic children in cities with mean 24-h average concentrations ranging from 16.8 to 64.5µg/m^3. Positive, but less consistent effects for respiratory symptoms and medication use were observed in asthmatic adults. One study examined the effects of PM_{10} on pulmonary inflammation, and observed an association between PM_{10} and exhaled nitrogen oxide (eNO). An evaluation of respiratory emergency department visits and hospital admission studies found consistent positive associations at ambient PM_{10} concentrations ranging from 13.3 to 60.8µg/m^3, among asthmatic children (~ 2% increase) and older adults with COPD (~ 0 to 3% increase). Although no toxicological or human clinical studies have examined the effect of short-term exposure to PM_{10} on respiratory morbidity, the consistent epidemiological evidence alone was sufficient for the USEPA (2009) to conclude that a causal relationship is likely to exist between short-term exposure to ambient concentrations of PM_{10} and respiratory morbidity.

3.7.2.3 Other morbidity outcomes

Worldwide, asthma is one of the most common chronic diseases of childhood. The underlying increased airways responsiveness that is inherent in asthma may increase

susceptibility to inhaled pollutants generally and particles specifically (WHO, 2006; OEHHA, 2001). The association between exposure to air pollution and asthma has been studied by tracking hospital admission and clinic visit rates and by panel studies of children that evaluate symptom status, medication use, or physiological indicators in relation to PM exposure. Delfino *et al. (321)* reported findings of a representative study of 19 California children who were tracked for two-week intervals with measurement of FEV1; personal exposures to particles were monitored as well. In Europe, the multicentre PEACE study addressed childhood asthma and air pollution, including particles *(322)*. While not all studies have linked particles to increased risk of exacerbation, the weight of evidence indicates that ambient particles do adversely affect children with asthma (WHO, 2006).

Epidemiological studies of asthmatic children have found increases in respiratory symptoms and asthma medication use associated with higher $PM_{2.5}$ or PM_{10} concentrations. Associations with respiratory symptoms and medication use are less consistent among asthmatic adults, and there is no evidence to suggest an association between respiratory symptoms with $PM_{2.5}$ among healthy individuals (USEPA, 2009). In addition, respiratory symptoms have not been reported following controlled exposures to $PM_{2.5}$ among healthy or health-compromised adults.

Although recent epidemiological studies of pulmonary function and $PM_{2.5}$ have yielded somewhat inconsistent results, the majority of studies have found an association between $PM_{2.5}$ concentration and FEV1, PEF, and/or MMEF. In asthmatic children, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ is associated with a decrease in FEV1 ranging from 1-3.4%. A limited number of controlled human exposure studies have reported small decreases in arterial oxygen saturation and MMEF following exposure to $PM_{2.5}$ concentrated ambient particles with more pronounced effects observed in healthy adults than in asthmatics or older adults with COPD (USEPA, 2009). In toxicological studies, changes in pulmonary function have been observed in healthy and compromised rodents after inhalation exposures to concentrated ambient particles from a variety of locations or diesel exhaust. A role for the particle component of diesel exhaust is supported by altered pulmonary function in healthy rats after IT instillation of diesel exhaust particles.

Several lines of evidence suggest that fine particles promote and exacerbate allergic disease, which often underlies asthma. Although epidemiological studies examining specific allergic outcomes and short-term exposure to particles are relatively rare, the available studies, conducted primarily in Europe, find positive associations between $PM_{2.5}$ and PM_{10} with allergic rhinitis or hay fever and skin prick reactivity to allergens. Short term exposure to diesel exhaust particles in controlled human exposure studies has been shown to increase the allergic response among previously sensitized atopic subjects, as well as induce de novo sensitization to an antigen. Toxicological studies continue to provide evidence that $PM_{2.5}$, in the form of concentrated ambient particles, resuspended diesel exhaust particles, or diesel exhaust, but not wood smoke, spurs and intensifies allergic responses in rodents. Proposed mechanisms for these effects include mediation by neurotrophins and oxidative stress, and one study demonstrated that effects were mediated at the epigenetic level (Liu *et al*., 2008).

A large body of evidence, primarily from toxicological studies, indicates that various forms of particles induce oxidative stress, pulmonary injury, and inflammation. Notably, concentrated ambient particles from a variety of locations induce inflammatory responses in rodent models, although this generally requires multiday exposures. The toxicology findings are consistent with several recent epidemiologic studies of $PM_{2.5}$ and the inflammatory marker eNO, which reported statistically significant, positive effect estimates

with some inconsistency in the lag times and use of medication. In asthmatic children, a 10 µg/m^3 increase in $PM_{2.5}$ is associated with an increase in eNO ranging from 0.46 to 6.99ppb. Several new controlled human exposure studies report traffic or diesel-induced increases in markers of inflammation (e.g., neutrophils and IL-8) in airway lavage fluid from healthy adults. Recent studies have provided additional evidence in support of a pulmonary oxidative response to diesel exhaust in humans, including induction of redox-sensitive transcription factors and increased urate and GSH concentrations in nasal lavage. In addition, exposure to wood smoke has recently been demonstrated to increase the levels of eNO and malondialdehyde in breath condensate of healthy adults (Barregard *et al*., 2008). Preliminary findings indicate little to no pulmonary injury in humans following controlled exposures to fine urban traffic particles or diesel exhaust, in contrast to a number of toxicological studies demonstrating injury with concentrated ambient particles or diesel exhaust.

Recent studies have reported associations between hospital admissions, emergency department or urgent care visits for several respiratory diseases with $PM_{2.5}$ components and sources including Ni, V, organic carbon and elemental carbon, wood smoke and traffic emissions, in studies of both children and adults. Delfino *et al*. (2003, 2006) found positive associations between organic carbon and elemental carbon components of particles and asthma symptoms and between elemental carbon and eNO. Particle composition and/or source also appears to heavily influence the increase in markers of pulmonary inflammation demonstrated in studies of controlled human exposures to $PM_{2.5}$. For example, whereas exposures to fine concentrated ambient particles from Chapel Hill, NC have been shown to increase BAL neutrophils in healthy adults, no such effects have been observed in similar studies conducted in Los Angeles. In addition, differential inflammatory responses have been observed following bronchial instillation of particles collected at different times or from different areas. One new study found that the increased airway neutrophils previously observed by Ghio *et al*. (2000) in human volunteers after Chapel Hill concentrated ambient particles exposure could be largely attributed to the content of sulfate, Fe, and Se in the soluble fraction (Huang *et al*., 2003).

Several epidemiological studies report associations between $PM_{10\text{-}2.5}$ and hospital admissions for respiratory disease with the most consistent evidence among children. Although a number of studies provide evidence of respiratory effects in older adults, a recent analysis of MCAPS data reports that weak associations of $PM_{10\text{-}2.5}$ with respiratory hospitalisations are further diminished after adjustment for $PM_{2.5}$. It is not clear that $PM_{10\text{-}2.5}$ estimates across all populations and regions are confounded by $PM_{2.5}$. An examination of $PM_{10\text{-}2.5}$ mortality associations on a national scale found a strong association between $PM_{10\text{-}2.5}$ and respiratory mortality, but this association varied when examining city-specific risk estimates (Zanobetti and Schwartz, 2009). Additionally, co-pollutant analyses were not conducted in this study, and the associations observed are inconsistent with those reported in single-city studies. There is greater spatial heterogeneity in $PM_{10\text{-}2.5}$ compared to $PM_{2.5}$ and consequently greater potential for exposure measurement error in epidemiological studies relying on central site monitors. This exposure measurement error may bias effect estimates toward the null.

Mar *et al*. (2004) provide evidence for an association with increased respiratory symptoms in asthmatic children but not asthmatic adults. Consistent with this, controlled human exposures to $PM_{10\text{-}2.5}$ have not been observed to affect lung function or respiratory symptoms in healthy or asthmatic adults. However, increases in markers of pulmonary inflammation have been demonstrated in healthy volunteers. In these studies, an increase in neutrophils in BAL fluid or induced sputum was observed, with additional evidence of

alveolar macrophage activation associated with biological components of $PM_{10-2.5}$ (i.e., endotoxin). Toxicological studies using inhalation exposures are still lacking, but pulmonary injury and inflammation have been observed in animals after IT exposure and both rural and urban $PM_{10-2.5}$ have induced these responses. In some cases, $PM_{10-2.5}$from urban air was more potent than $PM_{2.5}$ $PM_{10-2.5}$ respiratory effects may be due to components other than endotoxin (Wegesser and Last, 2008).

Overall, the most compelling evidence comes from a number of recent epidemiological studies conducted in Canada and France showing significant associations between respiratory emergency department visits or hospital admissions and short-term exposure to $PM_{10-2.5}$. Effects have been observed in areas where the mean 24-h avg $PM_{10-2.5}$ concentrations ranged from 7.4 to 13.0µg/m^3. The strongest relationships were observed among children, whereas studies of adults and older adults show less consistent evidence of an association. While controlled human exposure studies have not observed an effect on lung function or respiratory symptoms in healthy or asthmatic adults in response to exposure to $PM_{10-2.5}$, healthy volunteers have exhibited increases in markers of pulmonary inflammation. Toxicological studies using inhalation exposures are still lacking, but pulmonary injury has been observed in animals after intra-tracheal exposure to both rural and urban $PM_{10-2.5}$, which may not be entirely attributed to endotoxin. Overall, the USEPA (2009) concluded that epidemiological studies, along with the limited number of controlled human exposure and toxicological studies that examined $PM_{10-2.5}$ and respiratory outcomes, provide evidence that is suggestive of a causal relationship between short-term $PM_{10-2.5}$ exposures and respiratory effects.

3.7.3 Long term effects

Long-term exposure to $PM_{2.5}$ has been associated with health outcomes similar to those found in the short-term exposure studies, specifically for respiratory and cardiovascular morbidity and mortality. As found for short-term $PM_{2.5}$ exposure, the evidence indicates that a causal relationship exists between long-term $PM_{2.5}$ exposure and cardiovascular effects and that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and effects on the respiratory system (USEPA, 2009; WHO, 2006). The long-term exposure studies provide additional evidence for reproductive and developmental effects (i.e., low birth weights) and cancer (i.e., lung cancer mortality) in response to exposure to $PM_{2.5}$.

3.7.3.1 Mortality

The recent epidemiologic literature reports associations between long-term $PM_{2.5}$ exposure and increased risk of mortality in areas with mean $PM_{2.5}$ concentrations during the study period ranging from 13.2 to 29µg/m^3. When evaluating cause-specific mortality, the strongest evidence was found when examining associations between $PM_{2.5}$ and cardiovascular mortality, and positive associations were also reported between $PM_{2.5}$ and lung cancer mortality. The cardiovascular mortality association has been confirmed further by the extended Harvard Six Cities and American Cancer Society (ACS) studies, which both report strong associations between long-term exposure to $PM_{2.5}$ and cardiopulmonary and mortality from ischemic heart disease (Pope *et al*., 2004; Krewski *et al*; 2009; Laden *et al*., 2006). The most recent evidence for the association between long-term exposure to $PM_{2.5}$ and cardiovascular-mortality is particularly strong for women. Fewer studies evaluate the respiratory component of cardiopulmonary mortality, and the evidence to support an association with long-term exposure to $PM_{2.5}$ and respiratory mortality is limited (USEPA, 2009). The USEPA (2009) concluded that the evidence for cardiovascular and respiratory morbidity due to short- and long-term exposure to $PM_{2.5}$ provides biological plausibility for

cardiovascular- and respiratory-related mortality. Collectively, the evidence is considered to be sufficient to conclude that a causal relationship is likely to exist between long-term exposures to $PM_{2.5}$ and mortality.

A number of large, U.S. cohort studies have found consistent associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality. The American Cancer Society (ACS) (Pope *et al*. 2004) reported positive associations with deaths from specific cardiovascular diseases, particularly ischemic heart disease, and a group of cardiac conditions including dysrhythmia, heart failure and cardiac arrest (RR for cardiovascular mortality = 1.12 [95% CI: 1.08–1.15] per 10µg/m^3 $PM_{2.5}$). In an additional reanalysis that extended the follow-up period for the ACS cohort to 18 years (1982-2000) (Krewski *et al*., 2009), the effect estimates were similar, though generally higher, than those reported in previous ACS analyses. A follow-up to the Harvard Six Cities study (Laden *et al*., 2006) used updated air pollution and mortality data and found positive associations between long-term exposure to $PM_{2.5}$ and mortality. It is important to note that a statistically significant reduction in mortality risk was reported with reduced long-term fine particle concentrations. This reduced mortality risk was observed for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths.

The associations observed in the studies discussed above are supported by a large U.S.-based epidemiological study (i.e. Women's Health Initiative [WHI] study) that reports associations between $PM_{2.5}$ and cardiovascular disease among post-menopausal women using a 1-yr average $PM_{2.5}$ concentration (mean = 13.5µg/m^3). The WHI cohort study (Miller *et al*., 2007) found that each 10µg/m^3 increase of $PM_{2.5}$ was associated with a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76 [95% CI: 1.25–2.47]). The WHI study not only confirms the ACS and Six City Study associations with cardiovascular mortality in yet another well characterized cohort with detailed individual-level information, it also has been able to consider the individual medical records of the thousands of WHI subjects over the period of the study. This has allowed the researchers to examine not only mortality, but also related morbidity in the form of heart problems (cardiovascular events) experienced by the subjects during the study. These morbidity co-associations with $PM_{2.5}$ in the same population lend even greater support to the biological plausibility of the air pollution-mortality associations found in this study.

In an analysis for the Seventh-Day Adventist cohort in California (AHSMOG), a positive, association with coronary heart disease mortality was reported among females (92 deaths; RR = 1.42 [95% CI: 1.06–1.90] per 10 µg/m^3 $PM_{2.5}$), but not among males (53 deaths; RR = 0.90 [95% CI: 0.76-1.05] per 10µg/m^3 $PM_{2.5}$) (Chen *et al*., 2005). Associations were strongest in the subset of postmenopausal women (80 deaths; RR = 1.49 [95% CI: 1.17–1.89] per 10µg/m^3 $PM_{2.5}$). The results of this study are suggestive that females may be more sensitive to air pollution-related effects, based on differences between males and females in dosimetry and exposure (USEPA, 2009). As was found with fine particles, a positive association with coronary heart disease mortality was reported for $PM_{10\text{-}25}$ and PM_{10} among females (RR = 1.38 [95% CI: 0.97-1.95] per 10µg/m^3 $PM_{10\text{-}2.5}$; RR = 1.22 [95% CI: 1.01–1.47] per 10µg/m^3 PM_{10}), but not for males (RR = 0.92 [95% CI: 0.66–1.29] per 10µg/m^3 $PM_{10\text{-}2.5}$; RR = 0.94 [95% CI: 0.82–1.08] per 10µg/m^3 PM_{10}); associations were strongest in the subset of postmenopausal women (80 deaths) (Chen *et al*., 2005).

Two additional studies explored the effects of PM_{10} on cardiovascular mortality. The Nurses' Health Study (Puett *et al*., 2008) is an ongoing prospective cohort study examining the relation of chronic PM_{10} exposures with all-cause mortality and incident and fatal coronary

heart disease consisting of 66,250 female nurses in the north eastern region of the U.S. The association with fatal coronary heart disease occurred with the greatest magnitude when compared with other specified causes of death (hazard ratio 1.42 [95% CI: 1.11–1.81]). The North Rhine-Westphalia State Environment Agency (LUA NRW) initiated a cohort of approximately 4,800 women, and assessed whether long-term exposure to air pollution originating from motorized traffic and industrial sources was associated with total and cause-specific mortality (Gehring *et al*., 2006). They found that cardiopulmonary mortality was associated with PM_{10} (RR = 1.52 [95% CI: 1.09-2.15] per 10µg/m^3 PM_{10}).

Epidemiological studies that examined subclinical markers of cardiovascular disease report inconsistent findings. In addition, epidemiological studies have provided some evidence for potential modification of the $PM_{2.5}$-cardiovascular disease association when examining individual-level data, specifically smoking status and the use of anti-hyperlipidemics. Although epidemiological studies have not consistently detected effects on markers of atherosclerosis due to long-term exposure to $PM_{2.5}$, toxicological studies have provided strong evidence for accelerated development of atherosclerosis in ApoE-/- mice exposed to concentrated ambient particles and have shown effects on coagulation, experimentally-induced hypertension, and vascular reactivity (USEPA, 2009; WHO, 2006). Evidence from toxicological studies provides biological plausibility and coherence with studies of short-term exposure and cardiovascular morbidity and mortality, as well as with studies that examined long-term exposure to $PM_{2.5}$ and cardiovascular mortality. The USEPA (2009) concluded that taken together, the evidence from epidemiological and toxicological studies is sufficient to conclude that a causal relationship exists between long-term exposures to $PM_{2.5}$ and cardiovascular effects.

Two large U.S. cohort studies examined the effect of long-term exposure to $PM_{2.5}$ on respiratory mortality with mixed results. In the ACS study, Pope *et al*. (2004) reported positive associations with deaths from specific cardiovascular diseases, but no $PM_{2.5}$ associations were found with respiratory mortality. There is some evidence for an association between $PM_{2.5}$ and respiratory mortality among post-neonatal infants (ages 1 mo to 1yr). In summary, when deaths due to respiratory causes are separated from all-cause (non-accidental) and cardiopulmonary deaths, there is limited and inconsistent evidence for an effect of $PM_{2.5}$ on respiratory mortality, with one large cohort study finding a reduction in deaths due to respiratory causes associated with reduced $PM_{2.5}$ concentrations (Laden *et al*., 2006), and another large cohort study finding no $PM_{2.5}$ associations with respiratory mortality (Pope *et al*, 2004).

Multiple epidemiological studies have shown a consistent positive association between $PM_{2.5}$ and lung cancer mortality, but studies have generally not reported associations between $PM_{2.5}$ and lung cancer incidence (USEPA, 2009). Animal toxicological studies have examined the potential relationship between particles and cancer, but have not focused on specific size fractions of particles. Instead they have examined ambient particles, wood smoke, and diesel exhaust particles. A number of recent studies indicate that ambient urban particles, emissions from wood/biomass burning, emissions from coal combustion, and petrol and diesel exhaust are mutagenic, and that PAHs are genotoxic. These findings are consistent with earlier studies that concluded that ambient particles and particles from specific combustion sources are mutagenic and genotoxic and provide biological plausibility for the results observed in the epidemiological studies. A limited number of epidemiological and toxicological studies examined epigenetic effects, and demonstrate that particles induce some changes in methylation. However, it has yet to be determined how these alterations in the genome could influence the initiation and promotion of cancer. Collectively, the results

from epidemiological studies, primarily those of lung cancer mortality, along with the toxicological studies that show some evidence of the mutagenic and genotoxic effects of particles has led the USEPA to conclude that the evidence is suggestive of a causal relationship between long-term exposures to $PM_{2.5}$ and cancer.

The evidence from the daily time series studies and the prospective cohort studies is complementary in understanding the extent to which exposure to ambient particles shortens life. Associations observed in the time series studies could reflect only a brief advance in the time of death, perhaps among those already frail because of underlying heart and lung disease. This possibility, referred to as "harvesting" or "mortality displacement", implies that the associations observed in the daily time series studies are not indicating an effect of public health significance. The cohort studies provide information on a longer time frame and their positive findings suggest that the effect of particles on mortality is not a brief displacement of mortality. Analytical approaches to assessing the extent of mortality displacement have also been developed and results also indicate that any advance of the time of death caused by particles is more than just a few days (USEPA, 2009; WHO, 2006).

3.7.3.2 Morbidity

Recent epidemiological studies provide evidence of associations between long-term exposure to $PM_{2.5}$ and decrements in lung function growth, increased respiratory symptoms, and asthma development in study locations with mean $PM_{2.5}$ concentrations ranging from 13.8 to 30µg/m^3 during the study periods with effects becoming more precise and consistently positive in locations with mean $PM_{2.5}$ concentrations of 14µg/m^3 and above. These results are supported by studies that observed associations between long-term exposure to PM_{10} and an increase in respiratory symptoms and reductions in lung function growth in areas where PM_{10} is dominated by $PM_{2.5}$. However, the evidence to support an association with long-term exposure to $PM_{2.5}$ and respiratory mortality is limited (USEPA, 2009). Sub-chronic and chronic toxicological studies of concentrated ambient particles, diesel exhaust, air collected near roads and wood smoke provide coherence and biological plausibility for the effects observed in the epidemiological studies. These toxicological studies have presented some evidence for altered pulmonary function, mild inflammation, oxidative responses, immune suppression, and histopathological changes including mucus cell hyperplasia. Exacerbated allergic responses have been demonstrated in animals exposed to diesel exhaust and wood smoke. In addition, pre- and postnatal exposure to ambient levels of urban particles was found to affect lung development in an animal model. This finding is important because impaired lung development is one mechanism by which particle exposure may decrease lung function growth in children. The USEPA (2009) concluded that collectively, the evidence from epidemiological and toxicological studies is sufficient to conclude that a causal relationship is likely to exist between long-term exposures to $PM_{2.5}$ and respiratory effects.

Children may be at greater risk from long-term exposures to particles or other air pollutants because the growth and development of the respiratory system may be permanently affected by early environmental insults. The Southern Californian Children's Health Study was designed as a 10-year investigation of the impacts of southern California air pollution on lung growth and development and other indices of respiratory health among 3,676 fourth-, seventh-, and tenth-graders in 12 communities, which were chosen to emphasize different long-term air pollution conditions. For data collected in 1986-90, the 24-hr average PM_{10} concentration ranged from 28.0µg/m^3 in Atascadero and Santa Maria to 84.9µg/m^3 in Mira Loma and Riverside. In 1994, the mean 24-hr average PM_{10} concentration across the 12

communities was 34.8μg/m^3 (range = 13.0μg/m^3 in Lompoc to 70.7μg/m^3 in Mira Loma) (McConnell *et al*., 1999; Peters *et al*., 1999a).

At enrollment, neither PM_{10} nor $PM_{2.5}$ were associated with respiratory illness among the total cohort (ever or current asthma, bronchitis, cough, or wheeze) assessed by questionnaire (Peters *et al*., 1999a). In contrast, among children with asthma, respiratory symptoms increased with increasing particle levels (McConnell *et al*., 1999). Specifically, there was about a 40% increase in the odds of bronchitis among asthmatics per 19μg/m^3 change in PM_{10} measured over 2-week intervals (OR=1.4, 95% C.I. = 1.1-1.8). Exposure to a 15μg/m^3 increment in fine particles resulted in about the same magnitude of increase in risk, which was not statistically significant. Both measures of particles were also associated with at least a doubling of risk of phlegm in asthmatic children. Acid vapors and NO_2 were also associated with respiratory symptoms in asthmatic children. However, because PM_{10}, $PM_{2.5}$, NO_2, and acid vapor were highly correlated, it is not possible to definitively attribute these effects to any single pollutant (McConnell *et al*., 1999).

In another cross-sectional analysis of the Children's Health Study PM_{10} and $PM_{2.5}$, as well as NO_2, were significantly associated with decreased lung function (forced vital capacity [FVC], forced expiratory volume in one second [FEV1], and maximal mid-expiratory flow [MMEF]), especially in girls who spent more time outdoors (Peters *et al*., 1999b). These results were supported in an analysis of lung function growth over a four-year period (Gauderman *et al*., 2000). Examining the data from a sample of children who were fourth graders at enrollment, the investigators found statistically significant effects on lung function growth associated with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, and inorganic acid vapors. The effects were more pronounced for tests measuring airflow at low lung volumes, especially for children spending more time outdoors. There were no differences observed by gender. Although the effects on the children who were seventh- and tenth-graders at enrollment were generally also negative, these were not statistically significant, in part because the sample sizes in the higher grades were markedly smaller. As with the cross-sectional symptom data, the independent effects of the different pollutants cannot be assessed because of high inter-pollutant correlations.

The Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) examined the long-term effects of air pollution exposure in a cross-sectional study of 9,651 adults residing in eight areas in Switzerland in 1991. Eligibility for the study was conditional on having lived in the same area for at least three years. Particle measurements used in the analysis were taken over a 1-year period (1991 for TSP, and 1993 for PM_{10}), on the assumption that air pollution concentrations had not changed significantly over the proceeding several years. Significant associations were observed between chronic symptoms (chronic phlegm, chronic cough, breathlessness at rest during the day or at night, and dyspnea on exertion) and the pollutant metrics TSP, PM_{10} and NO_2 (Zemp *et al*., 1999). These associations were strongest for PM_{10}. The investigators estimated that an increase of 10μg/m^3 PM_{10} (within the observed range across cities of 10.1 – 33.4μg/m^3), would correspond to increases in risk among never smokers of 30% for chronic phlegm (OR=1.30, 95% C.I. = 1.04–1.63), 41% for breathlessness during the day (OR=1.41, 95% C.I. = 1.13–1.76), and 23% for dyspnea on exertion (OR = 1.23, 95% C.I. = 1.09–1.39). Nevertheless, the roles of PM_{10} versus NO_2 in the observed associations could not be ascertained, as NO_2 concentrations were strongly correlated with PM_{10} levels.

The SAPALDIA investigators also examined lung function (FEV1 and FVC) in study participants in relation to several air pollutants, controlling for age, sex, height, weight, atopy, educational level, nationality, smoking status (never, ever, and current), workplace exposures, residential gas stove, serious respiratory infection before age 5, and other potentially covariates (Ackermann-Liebrich *et al*., 1997). Statistically significant decrements in both indices of lung function were found in relation to annual mean levels of PM_{10}, sulfur dioxide, and nitrogen dioxide, with the strongest effects being related to PM_{10} (-3.4% for FVC and –1.6% for FEV1 in healthy never-smokers, per 10μg/m^3 annual average PM_{10}). The mean PM_{10} concentration in this study was 21.2μg/m^3, with a range of 10.1 – 33.4 μg/m^3. Similar, but slightly smaller, estimates were found for past and current smokers. As with the respiratory symptom analysis, however, the strong pollutant inter-correlations made it impossible to disentangle the effects of the various pollutants. The authors concluded that the principal source of all three pollutants, fossil fuel combustion, was associated with the decrements in lung function.

In summary, the evidence of particle effects in these studies of morbidity in relation to chronic exposures is not as consistent as for mortality. In several studies, the various particle measures are highly inter-correlated, or co-varied with gaseous pollutants, so that it was not possible to attribute the effects observed to any single pollutant or to a specific mix of pollutants. In studies examining effects of exposure to different particle measures, in some cases the point estimates of effect were greater for those metrics encompassing the coarse fraction and in some cases the reverse was true. Overall, there is some weak, evidence of a particle related effect on chronic morbidity, as measured by chronic respiratory symptoms and lung function. However, it is not possible, based on current evidence, to identify which size fractions or specific constituents are likely to be most influential (USEPA, 2009; OEHHA, 2001).

Evidence is accumulating for $PM_{2.5}$ effects on low birth weight and infant mortality, especially due to respiratory causes during the post-neonatal period. The mean $PM_{2.5}$ concentrations during the study periods ranged from 5.3–27.4μg/m^3 with effects becoming more precise and consistently positive in locations with mean $PM_{2.5}$ concentrations of 15μg/m^3 and above (USEPA, 2009). Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth weight than exposure to PM_{10}. The evidence from a few studies that investigated PM_{10} effects on foetal growth, which reported similar decrements in birth weight, provide consistency for the $PM_{2.5}$ associations observed and strengthen the interpretation that particle exposure may be causally related to reductions in birth weight. The epidemiological literature does not consistently report associations between long-term exposure to particles and preterm birth, growth restriction, birth defects or decreased sperm quality (USEPA, 2009). Toxicological evidence supports an association between $PM_{2.5}$ and PM_{10} exposure and adverse reproductive and developmental outcomes, but provided little mechanistic information or biological plausibility for an association between long-term particle exposure and adverse birth outcomes (e.g., low birth weight or infant mortality). Overall, the USEPA concluded that the epidemiological and toxicological evidence is suggestive of a causal relationship between long-term exposures to $PM_{2.5}$ and reproductive and developmental outcomes.

3.7.4 Threshold for effect

The exposure-response relationship has been extensively analysed primarily through studies that examined the relationship between particles and mortality. These studies, which have focused on both short- and long-term exposures to particles, have consistently found a

linear response and no safe threshold for effect (Daniels *et al*. 2004; Schwartz *et al*. 2004; Samoli *et al*. 2005; Schwartz *et al*. 2008). Although on a more limited basis, studies that have examined particle effects on cardiovascular hospital admissions and emergency department visits have also analysed the particle exposure-response relationship, and contributed to the overall body of evidence which suggests a log-linear, no-threshold particle exposure-response relationship.

Zanobetti and Schwartz (2005) conducted an extensive analysis of the shape of the exposure-response curve and the potential presence of a threshold when examining the association between PM_{10} and hospital admissions for myocardial infarction among older adults in 21 U.S. cities. The authors examined the exposure-response curve by fitting a piecewise linear spline with slope changes at 20µg/m^3 and 50µg/m^3. This approach resulted in an almost linear concentration-response relationship between PM_{10} and myocardial infarction hospital admissions with a steeper slope occurring below 50µg/m^3. There was no evidence for a threshold below which adverse effects were not observed. Overall, the limited evidence from the studies that examined the exposure-response relationship between particles and cardiovascular hospital admissions and emergency department visits supports a no-threshold, log-linear model, which is consistent with the observations made in studies that examined the particle-mortality relationship (USEPA, 2009; WHO, 2006).

3.7.5 Biological plausibility

Toxicological evidence is complementary to the observational findings of epidemiological studies, providing the framework for assessing the biological plausibility of observed associations. Studies designed to address the dose–response relationships can also inform the interpretation of exposure– response modelling of epidemiological data. Much toxicological research is now directed at identifying those characteristics of particles that determine toxicity (WHO, 2006).

Particles in inhaled air are deposited selectively throughout the respiratory tract at locations determined primarily by their size. Numerous sources of evidence show that inhaled particles have adverse consequences for the lungs and other organs.

Controlled exposure studies of humans and animals have shown that ambient particles or surrogate compounds, used to represent particles having particular characteristics, may have direct effects on the respiratory tract. These effects have mainly involved production of an inflammatory response, exacerbation of existing airway disease (e.g. hyperreactivity) or impairment of pulmonary defence mechanisms. Inhaled particles may increase the production of antigen-specific immunoglobulins, alter airway reactivity to antigens or affect the ability of the lungs to handle bacteria, suggesting that exposure may result in enhanced susceptibility to microbial infection (Zanobetti, *et al*., 2000).

Inflammation is considered central to producing many of the health effects attributed to particles (USEPA, 2009: WHO, 2006; OEHHA, 2001). Inflammation can be produced by oxidative stress via redoxsensitive transcription factors such as NF-κB, and numerous studies have demonstrated the ability of particles and surrogates to cause oxidative stress (Donaldson *et al*., 2003). In addition, a neurogenic mechanism has been suggested that might be mediated by C-reactive fibres and histamine (Nemmar *et al*., 2003; Nemmar *et al*. 1999). The expected cascade of molecular events has been demonstrated with particle exposure, including antioxidant depletion, NF-κB and AP-1 activation, Ca++ flux, kinase activation, phosphorylation of signalling molecules, gene expression and translation into protein of

pro-inflammatory cytokines and chemokines such as IL-8 and TNFα (Donaldson *et al*., 2003; Donaldson and Tran, 2004). In persons who are allergic, mechanisms related to the underlying disease process might also be relevant. Enhanced effects of particles are seen in asthmatics and allergic inflammation could be influenced by particles, as has been documented in animal models of inflammation (Dybing *et al*, 2004; Steerenberg *et al*, 1999; Steerenberg *et al*, 2003).

Genotoxic events underlie the carcinogenic effects of particles. Both direct, particle-mediated genotoxicity (Karlsson *et al*., 2004; Knaapen *et al*., 2002) and indirect genotoxic effects of inflammatory cells from particle-exposed animals (Knaapen *et al*., 1999) have been reproted. For cardiovascular outcomes, endothelial cells exposed to PM_{10} show changes indicative of enhancement of the potential for the endothelium to cause thrombosis (Gilmour *et al*., 2005). The respiratory tract is the portal of entry for inhaled particles and, consequently, clinical or subclinical effects in the respiratory tract may be reflected in subsequent events in other systems, or particles may be translocated outside of the respiratory tract without producing any observable pulmonary response (WHO, 2006).

One potential pathway for extrapulmonary effects of particles is via systemic transport of cytokines produced in the lungs during an inflammatory response (Brook, *et al*., 2003). Another potential pathway is through effects on coagulation properties that lead to increased risk of stroke or myocardial infarction (Peters *et al*., 2001). Particles may also result in endothelial and general vascular dysfunction (Brook *et al*., 2002) and chronic exposure may increase the progression of atherosclerosis (Kunzli *et al*., 2005). There is also the possibility that particles may have a direct effect on the heart, potentially through uptake of particles into the blood or through release of chemical components from particles into the circulation that affect either cardiac function or autonomic control of the cardiovascular system (WHO, 2006). Both parasympathetic and sympathetic pathways are involved in cardiac function. Stimulation of either of these by specific components of particles could affect blood pressure, heart rate and/or heart rate variability. Associations between these outcomes and exposure to particles have been observed in epidemiological studies (WHO, 2006).

3.7.6 Role of particle size and composition

Particles are classified according to size. In this section ultrafine particles refer to particles less that 0.1 μm mean aerodynamic diameter. The term fine particles relates to particles less than 2.5μm mean aerodynamic diameter, i.e. $PM_{2.5}$. Coarse particles are particles that range from 2.5-10 μm mean aerodynamic diameter, i.e, $PM_{10\text{-}2.5}$.

Evaluation of size mode alone as a modulating factor in particle toxicity is difficult since it is not independent of chemical composition, i.e. certain size modes tend to contain certain chemical components, such as metals in the fine mode and crustal materials in the coarse mode. Furthermore, there are clear differences between particles in different size modes in terms of total and regional dosimetry within the respiratory tract, and subsequent pathways and rates of translocation both within and outside of the respiratory tract (WHO, 2006; USEPA, 2009). Thus, the consequences of differing dosimetry may not be readily separable from those of differing characteristics.

Particle-size-dependent effects, independent of chemical composition, address the issue of a "nonspecific effect" of particle exposure, i.e. whether any biological effect of exposure is due to the particle's presence rather than to its specific chemistry. This question cannot be

answered unequivocally at present. Some studies have indicated that the enhancement of lipopolysaccharide-related lung injury by diesel exhaust particles could be attributed solely to the carbonaceous core of the particle, and not to any washed leachate or organic compound extract associated with the particle (Takano *et al*., 2002; Yanagisawa *et al*., 2003). In some studies, however, the coarse and fine fractions of particles were equally effective in producing release of inflammatory mediators, and the effects were greater than those produced by carbon black, suggesting that chemicals adsorbed on to the particle surface, rather than the presence of the particle itself, were responsible for toxicity (Pozzi *et al*., 2003).

For ultrafine particles, size itself rather than chemical composition may determine toxicity. Ultrafine particles appear to produce a more significant pulmonary inflammatory response than that produced by fine particles having the same chemical composition and at the same exposure mass concentration (Oberdorster *et al*., 1992; Li *et al*., 1996; Li *et al*., 1999; Li *et al*., 1997). For a given mass concentration ultrafine particles will have a greater number concentration than one consisting of fine particles, as well as a greater total surface area available for adsorption of toxic chemicals, therefore the exposure dose would actually be greater for ultrafine than for fine particles compared with other exposure metrics (WHO, 2006). WHO conclude that the enhanced biological effect from ultrafine particles may go beyond pulmonary inflammation, and may be relevant to systemic health outcomes found in epidemiological studies. For example, rats exposed to ultrafine carbon showed no evidence of pulmonary inflammatory response but did show extrapulmonary effects, including changes in the number of blood neutrophils, alteration of plasma thrombin–antithrombin complex and fibrinogen levels (Elder *et al*., 2004). However, the investigators could not conclude whether the observed effects were size- or chemical-specific. Similarly, rats exposed to ultrafine carbon particles showed increased heart rate and reduced heart rate variability, but no indication of an inflammatory response and no change in the expression of genes having thrombogenic relevance (Harder *et al*., 2005).

WHO (2006) proposed that a potential mechanism for enhanced effects of ultrafine particles may be the more effective translocation from the respiratory tract to extrapulmonary sites compared to larger particles. For example, ultrafine elemental carbon particles inhaled by rats were found in brain tissue, and were postulated to reach the brain via translocation along the olfactory nerve following deposition on the olfactory mucosa of the nasopharynx (Oberdorster *et al*., 2004). This pathway circumvents the protective blood–brain barrier of the central nervous system, and provides a direct route for inhaled particles into the nervous system without transport via the systemic circulation (WHO, 2006). A comparable pathway for translocation of soluble transition metal compounds has also been postulated (Tjalve and Henriksson, 1999; Arvidson, 1994; Dorman *et al*., 2002) but such a pathway may not be limited to ultrafine particles, as soluble manganese particles in the 1–2-µm size range appeared to translocate to the brain, specifically the olfactory bulb, following inhalation exposure (Dorman *et al*., 2004). Ultrafine particles have also been found to translocate from the respiratory tract to the liver (Nemmar *et al*., 2001; Oberdorster *et al*., 2002; Brown *et al*., 2002; Kreyling *et al*., 2002). Ultrafine particles may show greater toxicity than larger size modes owing to an enhanced ability to induce cellular damage by differentially affecting cellular organelles (Li *et al*., 2003).

Huang *et al*. (2003) exposed human bronchial epithelial cells to extracts of particles collected from ambient air in Taiwan, China, in three size ranges: $PM_{1.0}$ (<1 µm diameter), fine particles and coarse particles. The ability of particles to elicit inflammatory cytokine production and to cause lipid peroxidation was found to depend on particle size, being most evident for the ultrafine particles. The relationship between response and specific chemical

components was less defined, suggesting that the observed responses were associated either with different sets of particle components within each size mode or with nonspecific size effects (WHO, 2006). In a similar comparative study, using particles collected by ambient concentrators in the Los Angeles area, Li *et al*. (2003) examined differences in size and composition of ultrafine, fine and coarse particles in relation to uptake by macrophages and epithelial cells, and their ability to induce oxidative stress. On a per mass basis, the ultrafine particles were more potent than either the fine or coarse modes in this regard. However, it was not clear whether observed effects were due to particle size alone or to chemical characteristics, in that the ultrafine mode would have a higher number concentration and relatively larger surface area per unit mass for potential adsorption than would the larger size modes.

Asthmatic and healthy adults exposed to concentrated ambient particles in which 80% of the mass was coarse and the rest was <2.5µm showed increases in heart rate and decreases in heart rate variability *(*Gong *et al*., 2004*)*. Thus, in this study coarse particles may have had an effect on the autonomic nervous system.

In summary, WHO (2006) concluded that the available evidence provides a still equivocal answer to the question of a nonspecific role for particles in modulating toxicity and the extent to which size determines toxicity. The USEPA (2009) reached a similar conclusion. The determination of toxicity by physical size cannot be readily separated from other characteristics associated with size, such as chemical composition, number concentration or surface area. Even solubility may play a role in this regard, and solubility is another physical factor that differs between different particle size modes *(*Smith *et al*., 1998*)*. Characterizing the role of surface area is complex for particles because much of the mass is soluble salts, but for insoluble particles composed of low-toxicity material, the surface drives inflammatory responses *(*Duffin *et al*., 2001*)*. Furthermore, the specific bioactivity of ambient particles may actually depend on the relative proportion of soluble vs insoluble mass in the exposure atmosphere *(*Imrich *et al*., 2000*)*. For example, when particles were collected from various sites and tested for adjuvant activity, the water-insoluble fraction was generally more potent than the water-soluble fraction *(*Steerenberg *et al*., 2005*)*. Thus potential independent consequences of size and particle chemistry in determining toxicity cannot readily be separated (WHO, 2006; USEPA, 2009).

There is evidence that different particle components may target different biological systems (WHO, 2006). Thus, the combination of the biological endpoint examined along with the chemical component assessed may determine whether toxicity is observed. For example, Osornio-Vargas *et al*. (2003) exposed murine cells to PM_{10} and $PM_{2.5}$ recovered from filters sampling air in Mexico City to compare cytotoxic and proinflammatory effects of these two size fractions. The particles induced different biological effects depending on the specific sampling site and particle size. Toxicological studies have shown that the ultrafine, fine and coarse size modes may result in biological responses that could plausibly contribute to the health outcomes observed in epidemiological studies. The findings of epidemiological studies of acute and chronic health effects suggest that $PM_{2.5}$, which includes particles in the ultrafine size mode, is associated with a range of adverse health outcomes. However, there are only limited epidemiological data on either ultrafine or coarse particles to complement the toxicological studies of these size fractions.

The toxicological studies provide evidence that aspects of particles other than mass alone determine toxicity. In terms of chemical species, the strongest toxicological consistency is with secondary inorganic particles, namely sulfates and nitrates at above-ambient levels, but

this consistency is opposed by a lack of effect in controlled exposure studies within the ambient concentration range (WHO, 2006). The findings of the controlled exposure studies contrast with some of the epidemiological findings. There are many potential explanations for this lack of coherence across different lines of investigation and research is required to investigate this further. Controlled exposure studies strongly suggest that transition metals are a chemical component of particles with toxic potential. Experimental studies generally used fairly high exposure concentrations, leaving the relevance of their findings to ambient exposure unclear. Furthermore, the concentration of such metals varies widely geographically, but is generally quite low in ambient air. A potential role for transition metals at relatively high concentrations in determining risk for health outcomes was demonstrated in parallel toxicological studies and in epidemiological studies of particles associated with steel mill emissions in the Utah Valley. However, recent long-term exposure toxicology suggests that acute biological effects may be due to transition metals at lower ambient concentrations (Maciejczyk and Chen, 2005).

Experimental studies have indicated that the organic constituents of particles are also likely to be toxicologically active. While the current evidence is not sufficient to develop an unequivocal conclusion as to risk from specific organic compounds, the PAHs or their nitro- and oxyderivatives have been identified as potential toxic components. Most studies with biogenic organic carbon-containing aerosols examined bacterial endotoxin, a cell wall component. Endotoxin is present in the coarse mode and may be responsible, at least in part, for the toxicity of this size mode observed in some studies (WHO, 2006).

In summary from the currently available toxicological evidence, there is little indication that any single physical or chemical property of particles is responsible for the array of adverse health outcomes reported in epidemiological studies (WHO, 2006). The public health consequences in any particular location may reflect the particular characteristics of particles generated by the mix of local and regional sources. Toxicological studies do, however, indicate that primary particles generated from fossil fuel combustion processes may be a significant contributor to adverse health outcomes. These emissions generally have a high content of organic carbon and some metals, and may have large surface area and number concentration. However, WHO (2006) concluded that the evidence cannot support an indicator for a standard that is more specific than size fractionated mass alone.

3.7.7 Findings of the review of the particles health evidence

There is substantial new evidence from time series studies of daily mortality, particularly from multi-city studies that span Europe and North America. Since the NEPM was made in 1998 there have been several studies conducted in Australia that also show adverse effects of both PM_{10} and $PM_{2.5}$ on mortality and morbidity outcomes. The effect estimates observed in the Australian studies appear to b higher that those observed in the US and Europe but comparable to the results of Canadian studies. The epidemiological evidence is supported by an increasingly strong foundation of toxicological research. Various mechanisms have been proposed by which particles may cause and/or exacerbate acute and chronic diseases. Inflammation due to the production of reactive oxygen species is emerging as a central mechanism. The most results of toxicological studies have found that specific characteristics cannot yet be identified as critical for toxicity.

The contribution of ambient particles to personal exposures has extensively studied and the results show that ambient particles contribute substantially to personal exposures even though most time is spent indoors. The exposure assessment studies have also provided

evidence supporting the use of ambient particle concentration as an indicator of population exposure to particles in epidemiological studies. The evidence does not lead to the use of any specific indicator beyond either PM_{10} or $PM_{2.5}$, both size fractions of particles that enter the respiratory tract. At this stage there is no conclusive evidence for the toxicity of ultrafine particles that would form the basis for a standard for this size fraction. In addition there is no data available in Australia that could be used to guide the development of a standard.

There is increasing evidence that the coarse fraction, $PM_{10-2.5}$ is associated with adverse health effects. This may be of particular importance in Australia given the large contribution of coarse particles from dust to PM_{10}. However, there is no data available at this time on ambient levels of $PM_{10-2.5}$ that could be utilised to guide the development of a standard.

The evidence that has arisen since the NEPM was made in 1998 reaffirms the adverse consequences of air pollution for population health and supports an independent role of particles in causing adverse health effects. This independent role has been documented through epidemiological studies that have carefully disentangled the effect of particles from the potentially confounding effects of other pollutants, and by toxicological studies that have demonstrated mechanisms by which particles may cause adverse health effects.

3.7.7.1 Implications of the health evidence for particles NEPM standard

For various health outcomes, there has not been any indication of a threshold below which adverse effects would not be observed. The lack of an apparent threshold for adverse health effects poses a substantial barrier for proposing standards that protect the public against such effects.

The evidence also excludes the possibility of implementing standards that would protect against adverse health effects with a high degree of certainty. To provide a mechanism whereby the risk of adverse health effects is reduced a combination of approaches may be required. For example European Union countries have introduced an exposure reduction approach for $PM_{2.5}$. This approach together with a standard provides a mechanism whereby exposure and risk can be reduced while still setting a minimum standard that must be met. This approach has been discussed in a previous discussion paper as part of this review (NEPC, 2007, www.ephc.gov.au) and also in section 4.3 of this discussion paper.

3.8 Benzene

Although not previously considered as criteria pollutants, benzene and PAHs, arise from many sources and are ubiquitous in the environment. They are currently covered in Australia by the Air Toxics NEPM. In the previous discussion paper developed for this review, there issue of whether these pollutants should be included in the AAQ NEPM was raised. There strong support during consultation for this to occur. Therefore, below are brief summaries of the health effects attributed to benzene and PAHs should a decision be made by NEPC to move them to the AAQ NEPM as advocated by stakeholders.

3.8.1 Introduction

The adverse health effects of benzene exposure have been assessed by numerous agencies NEPC, 2004; NICNAS (2001); WHO (2000); International Program on Chemical Safety, (1993); Commission of European Communities, (1998); United Kingdom Expert Panel on Air Quality Standards, (1994); US EPA (2000); Environment Canada (1993). The most recent

review was completed by Agency for Toxic Substances and Disease Registry (ATSDR) in 2007 which confirmed the findings of previous reviews.

The critical human health effects from long term exposure to benzene are bone marrow depression and leukaemia, specifically acute non-lymphocytic leukaemia (also known as acute myeloid leukaemia). Benzene is classified as a known human carcinogen. It is considered to be a genotoxic carcinogen for which no threshold has been established. (ATSDR, 2007; NICNAS 2001, US EPA 2000, WHO 2000).

There are five key occupational cohort studies demonstrating an association between benzene and an increase in the incidence of leukaemia for which the exposures have been assessed in detail. These are the Goodyear Pliofilm (Rinsky *et al*, 1981), the Chemical Manufacturers Association (CMA), (Wong, 1987a, 1987b), Dow Chemical (Bond *et al*, 1986), the Chinese Shoe Worker study (Lan *et al*, 2004a; 2004b) and the Chinese Factory Worker (Hayes *et al*, 1997) cohorts. Most assessments have considered that the analyses of the Goodyear Pliofilm study has given them the most robust database on which to base their assessments of benzene concentrations associated with development of leukemia and the degree of risk. The latest Minimal Risk Levels developed by the ATSDR (2007) are based on the Chinese Shoe Worker studies (Lan *et al*., 2004a; 2004b).

Recent meta-analyses have found an association between exposure to benzene and Non-Hodgkin's Lymphoma (NHL) (Steinmaus *et al*., 2008). A meta-analysis of cohort and case-control studies of benzene exposure and NHL and a meta-analysis of NHL and refinery work, a potential source of benzene exposure were performed. In 22 studies of benzene exposure, the summary relative risk for NHL was 1.22 (95% CI 1.02 to 1.47; one-sided p value = 0.01). When studies that likely included unexposed subjects in the "exposed" group were excluded, the summary relative risk increased to 1.49 (95% CI 1.12 to 1.97, n = 13), and when studies based solely on self-reported work history were excluded, the relative risk rose to 2.12 (95% CI 1.11 to 4.02, n = 6). In refinery workers, the summary relative risk for NHL in all 21 studies was 1.21 (95% CI 1.00 to 1.46; p = 0.02). When adjusted for the healthy worker effect, this relative risk estimate increased to 1.42 (95% CI 1.19 to 1.69). The authors concluded that the finding of elevated relative risks in studies of both benzene exposure and refinery work provides further evidence that benzene exposure causes NHL. In addition, the finding of increased relative risks after removing studies that included unexposed or lesser exposed workers in "exposed" cohorts, and increased relative risk estimates after adjusting for the healthy worker effect, suggest that effects of benzene on NHL might be missed in occupational studies if these biases are not accounted for.

Most of the human health-exposure data have been obtained from retrospective epidemiological studies relating to occupational settings. It is accepted that there are difficulties in relating these studies usually in fit, healthy adults to the population in general, which consists of all ages and various levels of health and infirmity.

3.8.2 Key International Studies

Most of the information on the health effects of benzene have been found in international studies. Only one new study has been identified since the latest review conducted by the ATSDR (2007). The key studies are summarised below. No studies have been conducted in Australia.

3.8.2.1 The Goodyear Pliofilm cohort

An excess incidence of leukaemia in rubber workers at two Goodyear facilities in Ohio, USA was reported in a preliminary paper by Infante *et al*. (1977) and in more detail by Rinsky *et al*. (1981). Depending on its definition, this cohort comprises 1165-1212 male workers employed from 1936–75 in the manufacture of Pliofilm. The manufacturing process used large volumes of benzene as a solvent and there was no exposure to other known carcinogenic substances. Excluding deaths before 1950, Rinsky *et al*. (1987) identified 15 deaths from lymphatic and haematopoietic cancers versus 6.6 expected (Standardised Mortality Rate {SMR} = 2.27 {1.27–3.76}) and 9 deaths from leukaemia versus 2.7 expected (SMR = 3.37 {1.54-6.41}).

3.8.2.2 The Chemical Manufacturers Association (CMA) cohort study

This is a study of 4602 male chemical workers who were employed for ≥6 months from 1946-75 at 7 US plants (Wong, 1987a, 1987b). Two comparison groups were used: the general US population and 3074 unexposed male workers employed at the same plants at the same time as the cohort. The vital status of all subjects was followed until the end of 1987 and the findings compared to average and peak exposures as determined from available air monitoring data and employment records obtained from the participating companies. There were 19 deaths from cancer of the blood and lymphatic system in the exposed workers compared to 3 in the unexposed group. In the exposed group, 7 of the observed cases were diagnosed with leukaemia and the remaining 12 with lymphoma. In the unexposed workers, all 3 cases were diagnosed with lymphoma, there were no cases of leukaemia in the unexposed workers. The SMRs for all cancers of the blood and lymphatic system were 0.91, 1.47, and 1.75, and for leukaemia 0.97, 0.78 and 2.76 for cumulative exposures of less than180, 180-719 or ≥720ppm-months respectively, but none of the ratios was significantly different from unity. The trend for all cancers of the blood and lymphatic system was significant (p = 0.02), and (p = 0.01) for leukaemia for trend with cumulative exposure.

3.8.2.3 The Dow Chemical cohort

This study comprised 956 male chemical workers employed at a single site in Michigan, USA, between 1940 and 1982. The workers were exposed to benzene in chlorobenzene or alkylation plants which used benzene as a raw material, or in an ethyl cellulose plant where benzene was used as a solvent (Bond *et al*, 1986; Ott *et al*, 1978). Each job entry was assigned an exposure intensity level on the basis of job classification and representative personal air monitoring data. There were 6 deaths from cancer of the blood and lymphatic system against 4.8 expected, including 4 cases of myelogenous leukaemia against 0.9 expected. The excess of myelogenous leukaemia was statistically significant (p = 0.011; SMR and 95% CI not stated).

3.8.2.4 US National Cancer Institute (NCI) and Chinese Academy of Preventive Medicine (CAPM) Chinese factory workers cohort study

A follow up on a large cohort study commenced in 1982 to assess the risks of specific bone marrow disorders in relationship to occupational benzene exposure (Hayes *et al*, 1997). The final cohort comprises 74,828 male and female benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities in China and 35,805 unexposed workers. Relative risks (RRs) were determined for incident cancer of the blood and lymphatic system, non-Hodgkin's Lymphoma (NHL), leukaemia, Acute non-lymphatic leukaemia (ANLL), a

diagnosis of either ANLL or Myelo Dysplastic Syndromes (MDS), and leukaemia other than ANLL, with stratification by age and sex. The exposed workers held permanent jobs in the painting, printing, footwear, rubber and chemical industries. Exposure levels were estimated from available area monitoring data, detailed production and process information, and employee records.

There were 58 specified cancers of the blood and lymphatic system and 18 other bone marrow disorders (2 cases of agranulocytosis, 9 of aplastic anaemia and 7 of MDS) in the cohort, compared to 13 and 0 respectively in the control group.

When the cohort was divided into three categories, according to the estimated cumulative benzene exposure level, the RR for all cancer of the blood and lymphatic system was elevated from <40ppm-years 2.2 (1.1-4.5). The RRs for leukaemia was elevated from 40–99ppm-years 3.1 (1.2-8.0), and ANLL/MDS from 40–99ppm-years 6.0 (1.8-20.6).

3.8.2.5 The Chinese Shoe Worker Study

A cross-sectional study (Lan *et al*. 2004a, 2004b) was performed on 250 workers exposed to benzene in shoe manufacturing industries in Tianjin, China, and 140 age- and gender-matched workers in clothing manufacturing facilities that did not use benzene. The benzene-exposed workers had been employed for an average of 6.1±2.9 years. Controls consisted of 140 age-and gender-matched workers in clothing manufacturing facilities in which measurable benzene concentrations were not found (detection limit 0.04ppm). Benzene exposure was monitored by individual monitors (full shift) 5 or more times during 16 months prior to phlebotomy. Benzene-exposed workers were categorized into four groups (controls, <1, 1–<10, and ≥10ppm) according to mean benzene exposure levels measured during 1 month prior to phlebotomy. Complete blood count (CBC) and differential were analysed mechanically. Coefficients of variation for all cell counts were <10%.

Mean 1-month benzene exposure levels in the four groups (controls, <1, 1–<10, and ≥10ppm) were <0.04, 0.57±0.24, 2.85±2.11, and 28.73±20.74ppm, respectively. Haematological values were adjusted to account for potential confounding factors (i.e., age, gender, cigarette smoking, alcohol consumption, recent infection, and body mass index). All types of WBCs and platelets were significantly decreased in the lowest exposure group (<1ppm), ranging in magnitude from approximately 8 to 15% lower than controls. Although similar statistical analyses for the mid- and high-exposure groups were not included in the study report, decreases in all types of WBCs and platelets were noted at these exposure levels as well; the decreases in the highest exposure group ranged in magnitude from 15 to 36%. Lymphocyte subset analysis revealed significantly decreased CD4+-T cells, CD4+/CD8+ ratio, and B cells. Haemoglobin concentrations were significantly decreased only within the highest (≥10ppm) exposure group. Tests for a linear trend using benzene air level as a continuous variable were significant for platelets and all WBC measures except monocytes and CD8+-T cells. Upon restricting the linear trend analyses to workers exposed to <10ppm benzene, excluding controls, inverse associations remained for total WBCs, granulocytes, lymphocytes, B cells, and platelets.

In order to evaluate the effect of past benzene exposures on the haematological effects observed in this study, the authors compared findings for a group of workers who had been exposed to <1ppm benzene over the previous year (n=60) and a subset who also had <40ppm-years lifetime cumulative benzene exposure (n=50). The authors stated that the

same cell types were significantly reduced in these groups, but did not provide further information of the magnitude (i.e., percent change) of the haematological effects observed. These data suggest that the 1-month benzene exposure results could be used as an indicator of longer-term low-level benzene haematotoxicity. To demonstrate that the observed effects were attributable to benzene, significantly decreased levels of WBCs, granulocytes, lymphocytes, and B cells were noted in a subgroup (n=30; mean 1-month exposure level of 0.29±0.15ppm) of the <1ppm group for which exposure to other solvents was negligible. Lan *et al*. (2004a, 2004b) also presented information on the effect of benzene on colony forming progenitor cells (data were only presented for the mid- and high-exposure groups). Benzene exposure was associated with a concentration-dependent decrease in colony formation and progenitor cells were suggested to be more sensitive than circulating cells.

3.8.3 Modes of action

Several reviews of benzene metabolism and the proposed mechanisms of toxicity have been published (Ross, 1996; Snyder, 2000; Snyder *et al*, 1993; Snyder & Hedli, 1996; Yardley-Jones *et al*, 1991).

Exposure to benzene can result in haematotoxicity, immunotoxicity and carcinogenicity in humans and animals. Haematotoxicity resulting from chronic benzene exposure can present as anaemia, aplastic anaemia, leukopenia, lymphocytopenia, thrombocytopenia, or pancytopenia (Aksoy, 1989). While the liver is the initial site for the biotransformation of benzene, hepatotoxicity is not a consequence of benzene exposure. Subsequently, these metabolites become localised within the bone marrow (Rickert *et al*, 1979) where they undergo activation by peroxidase enzymes, which are present in bone marrow. While individual benzene metabolites appear not to induce bone marrow toxicity, the combination of phenol and hydroquinone has been shown to induce the same effects on bone marrow as benzene (Eastmond *et al*, 1987). This effect appears to be due to the ability of phenol to act as a co-oxidant in the activation of metabolites.

Subsequent changes in cellular function result in altered growth factor production with inhibition of bone marrow stem cell proliferation, differentiation and maturation. The formation of reactive oxygen species damage cells and result in DNA adduct formation, DNA base modification, chromosomal aberrations that can lead to cellular damage which may result in leukaemia in humans or solid tumours in animals.

3.8.4 Non cancer endpoints

3.8.4.1 Effects of long term human exposure

Tsai *et al* (1983) examined the mortality from all cancers and leukaemia, in addition to haematological parameters in 454 male workers exposed to benzene for 1-21 years in a refinery from 1952–1978. The median air concentration was 0.53ppm in the work areas of greatest exposure to benzene. The average length of employment in the cohort was 7.4 years. The analysis of overall mortality in this population revealed no significant excesses. A subset of 303 workers was followed for medical surveillance. Up to four haematological tests per year showed all parameters to be within normal limits in this group.

Collins *et al*. (1997) used routine data from Monsanto's medical/industrial hygiene system to study 387 workers with daily 8-hour time-weighted exposures (TWA) averaging 0.55ppm benzene (range = 0.01–87.69ppm; based on 4213 personal monitoring samples, less than 5%

of which exceeded 2ppm). There was no increase in the prevalence of lymphopenia (decreases in lymphocyte numbers), an early, sensitive indicator of benzene toxicity, or other measures of haematotoxicity.

Rothman *et al* (1996) studied a small number (44) of Chinese workers heavily exposed to benzene (31ppm, 2–329ppm range) and showed decreases in white blood cell counts and absolute lymphocyte counts and other blood parameters when compared to matched unexposed controls. In a much smaller subgroup of 11 of the 44 workers, with a recorded lower median exposure to benzene of 7.6ppm (1–20ppm range), only the absolute lymphocyte count was decreased compared to the controls. Their results support the use of the absolute lymphocyte count as the most sensitive indicator of benzene-induced haematotoxicity.

3.8.5 Summary of benzene non-cancer health effects

The No Observed Adverse Effect Level (NOAEL) for haematotoxicity in humans was established by Tsai *et al* (1983) at 0.53ppm, and by Collins *et al* (1997) at 0.55ppm, from long-term worker exposure studies, with daily 8 hours exposures, 5 days per week. NICNAS (2001) also conclude NOAELs to be around the 0.5ppm level and a LOAEL (lowest observed adverse effect level) at 7.6ppm in a subgroup of 11 exposed workers (Rothman *et al* 1996).

Although the study by Tsai *et al.* (1983) is a freestanding NOAEL of 0.53ppm, the endpoint examined is a known sensitive measure of benzene toxicity in humans. The recent results of Collins *et al*. (1997) that included a NOAEL of 0.55ppm and of Rothman *et al* (1996) that included a LOAEL of 7.6ppm are consistent with those of Tsai *et al*. (1983).

3.8.6 Effects of laboratory animal exposure to benzene

A number of animal studies have demonstrated that benzene exposure can induce bone marrow damage Ward *et al* (1985), Keller and Snyder (1978), changes in circulating blood cells, Aoyama (1986), developmental and reproductive effects Kuna and Kapp (1981), and cancer at multiple organ sites. With respect to long term exposure toxicity, haematological changes appear to be the most sensitive indicator.

3.8.7 Findings of the review of the benzene health evidence

The health effects of benzene are well documented. Benzene is a known human carcinogen linked specifically to cases of acute myeloid leukaemia. There is no known threshold for carcinogenic effects. Recent studies including a meta-analysis of 22 studies have found benzene exposure linked to increases in non-Hodgkin's lymphoma (NHL) (RR 1.22). In addition to carcinogenic effects, exposure to benzene has also been linked with haematological changes including decreases in white blood cells and platelets.

The significant body of evidence on the health effects of benzene has resulted in international air quality standards for benzene that currently stand at 1.5ppb as an annual average. This value been adopted in EU legislation and applies in all EU member countries. The UK has adopted it into their air quality strategy. Japan, Canada and India have all adopted 1.5ppb or are considering it at this time as a regional air quality objective.

The current national air quality standard for benzene is contained in the Air Toxics NEPM as a monitoring investigation level (MILs). The MILs are not ambient air quality standards

as contained in the AAQ NEPM, but are trigger levels for further investigation and action that apply at hot-spots. If benzene is moved to the AAQ NEPM then the MIL would need to be assessed to ensure that the level of protection as a regional air quality standard is appropriate.

3.9 Polycyclic Aromatic Hydrocarbons

3.9.1 Introduction

The health effects of polycyclic aromatic hydrocarbons (PAHs) have been reviewed extensively (NEPC, 2004; EC, 2001; WHO, 2000; OEHHA, 1999; UK EPAQS, 1999; IPCS, 1998; ATSDR, 1995; Env. Canada, 1994). One of the complexities in evaluating the health effects of PAHs is that they exist as a mixture of compounds not individual compounds. The toxicity of these compounds varies quite markedly, with the most toxic being benzo(a)pyrene (BaP), which is classified as a carcinogen.

There is little information on human exposure to single, pure PAH. That which is available includes reports of accidental exposure to naphthalene and some data from defined short-term studies of volunteers. All other reports are of exposure to mixtures of PAH, which also contained other (non-PAH) potentially carcinogenic chemicals, in occupational and environmental situations.

Several epidemiological studies have shown increased mortality due to cancer, which has been associated with exposure to PAH-containing mixtures in humans exposed to coke oven emissions, roofing-tar emissions, and cigarette smoke. The cancers occur predominantly in the lungs and skin following inhalation and dermal exposure, respectively but can occur in other tissues away from the major route of exposure. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens, and the potential interactions that could occur with other toxic substances in the mixtures. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene to cause cancer in humans.

The critical endpoint for health risk evaluation is the well-documented carcinogenicity of several PAHs (IARC 1983). BaP is by far the most extensively studied PAH in experimental animals. It produces tumours of many different tissues, depending on the species tested and the route of application. BaP is the only PAH that has been tested for carcinogenicity following inhalation, and it produced respiratory tract tumours (not lung tumours) in hamsters, the only species tested (Thyssen *et al*, 1981). Induction of lung tumours in rats and hamsters has also been documented for BaP and several other PAHs following direct application, such as intratracheal instillation into the pulmonary tissue (Deutsch-Wenzel *et al*, 1983).

The lung carcinogenicity of BaP can be enhanced by co-exposure to other substances such as cigarette smoke, asbestos and airborne particles. Several studies have shown that the benzene-soluble fraction, containing 4 to 7-ring PAHs of condensates from car exhausts, domestic coal-stove emissions and tobacco smoke, contains nearly all the carcinogenic potential of PAHs from these sources (Pott & Heinrich, 1990).

Because several PAHs have been shown to be carcinogenic, and many more have been shown to be genotoxic in *in vitro* assays, a suitable indicator for the carcinogenic fraction of the large number of PAHs in ambient air is desirable. The most appropriate indicator for the carcinogenic PAHs in air seems to be BaP concentrations, given present knowledge and the existing database.

The proportion of different PAHs detected in emissions and in workplaces differs widely from each other and from PAH profiles in ambient air. Nevertheless, the profiles of PAHs in ambient air do not seem to differ very much from one area to another, although large variations may be seen under special conditions. Furthermore, the carcinogenicity of PAH mixtures may be influenced by synergistic and antagonistic effects of other compounds emitted together with PAHs during incomplete combustion. It should also be recognised that in ambient air, the carcinogenic 4 to 7-ring PAHs (representing the majority of PAHs) are solids and are preferentially attached to particles and only a minor fraction, depending on the temperature, exist as volatiles. A few studies indicate that the toxicokinetic properties of inhaled BaP attached to particles are different from those of pure BaP alone. Virtually nothing is known about other PAHs in this respect.

WHO presented an excess lifetime cancer risk, expressed in terms of the BaP concentration and based on observations in coke oven workers exposed to mixtures of PAHs. It was emphasised that the composition of PAHs to which coke oven workers are exposed may not be similar to that in ambient air.

The WHO adopted the lung cancer risk estimate calculated by the US Environmental Protection Agency. The US EPA based its calculations on extensive studies of coke oven workers in Pennsylvania. The US EPA used a linearised multistage model.

The unit risk for BaP is estimated to be 8.7×10^{-5} $(ng/m^3)^{-1}$. The corresponding concentrations of BaP producing excess lifetime cancer risks of 1/10 000, 1/100 000 and 1/1 000 000 are 1.2, 0.12 and 0.012ng/m^3 respectively.

3.9.2 Key International studies

The epidemiological study by Armstrong *et al* (1994) of lung cancer deaths in men who had worked in an aluminium smelter in Canada is considered a key study into the health effects of PAHs as it addressed the confounder of smoking. In this investigation exposure to BaP as a marker of PAH exposure (benzene soluble coal tar pitch volatiles) was estimated for workers in each type of job within the plant. The heaviest exposure occurred for workers in two parts of the process known as 'the pot room' and 'anode manufacture', where BaP concentrations were 20–40µg/m^3. After adjustment for confounding by cigarette smoking and age, a clear association was found between increased exposure to BaP and lung cancer deaths RR 2.23 (95% CI 1.46–3.39) at 100–199µg/m^3-years of BaP.

Costantino *et al* (1995) reported a significantly increased risk for lung cancer (SMR, 1.95 with 95% CI of 1.59–2.33) among a cohort of over 5000 workers who were heavily exposed at coke ovens in coke plants and were followed-up for over 30 years. The authors concluded that 124 deaths from lung cancer occurred among these coke-oven workers that could be attributed to exposure to coal-tar pitch volatiles, (2.3% of the cohort). Although no data were available on smoking habits, the observed effect is not likely to be due to smoking since unexposed steel workers in a comparison group were assumed to have similar

smoking habits. In addition, a high correlation was seen between the risk for respiratory cancer and the concentration and duration of exposure.

The respiratory health of 667 workers in a rubber factory was investigated (Gupta *et al* 1993). Respiratory health was evaluated and examined for correlations to length of employment at the factory. In addition, total suspended particulate matter and benzo(a)pyrene concentrations were monitored in various parts of the factory and examined for possible correlation with the respiratory health of the workers in the same area of the factory. Statistically significant decrements in ventilation function occurred following prolonged exposure as assessed by duration of employment. When different sections of the factory were considered, workers in the compounding section were the most affected, which was associated with the highest exposure to particulate matter and benzo(a)pyrene. Workers in the compounding section exhibited radiographic abnormalities including patch opacities, prominent bronchiovascular markings, and pleural effusions. Other symptoms included bloody vomit, breathing problems, chest pains, chest irritation, throat irritation, and cough. Workers in other areas of the plant exposed to lower levels of particulate matter and benzo(a)pyrene were similarly affected although to a lesser degree and in fewer numbers. No attempt was made to separate the effects of exposure to benzo(a)pyrene and particulate matter, or to identify possible simultaneous exposure to other toxic chemicals.

A study has been conducted in Canada to estimate the exposure-response function associating polycyclic aromatic hydrocarbon (PAH) exposure and lung cancer, controlling for the effects of smoking (Friesen *et al*., 2009). Mortality, occupational exposure and smoking histories were ascertained for a cohort of 16,431 persons (15,703 men and 728 women) who had worked in one of four aluminium smelters in Quebec from 1950 to 1999. A variety of exposure-response functions were fitted to the cohort data using generalised relative risk models. In 677 lung cancer cases there was a clear trend of increasing risk with increasing cumulative exposure to PAH measured as benzo(a)pyrene (BaP). A linear model predicted a relative risk of 1.35 (95% CI 1.22 to 1.51) at 100μg/m^3 BaP years, but there was a significant departure from linearity in the direction of decreasing slope with increasing exposures. Among the models tried, the best fitting were a two-knot cubic spline and a power curve (RR = (1+bx)(p)), the latter predicting a relative risk of 2.68 at 100 BaP μg/m^3 years. Additive models and multiplicative models for combining risks from occupational PAH and smoking fitted almost equally well, with a slight advantage to the additive. Despite the large cohort with long follow-up, the shape of the exposure-response function and the mode of combination of risks due to occupational PAH and smoking remains uncertain. The authors found that if a linear exposure-response function is assumed, the estimated slope was broadly in line with the estimate from a previous follow-up of the same cohort, and somewhat higher than the average found in a recent meta-analysis of lung cancer studies.

Although several toxicological and epidemiological studies have produced evidence that occupational exposure to polycyclic aromatic hydrocarbons (PAH) is a risk factor for ischemic heart disease (IHD) a clear exposure-response relation has not been demonstrated. A multi-city study has examined the relation between exposure to PAH and mortality from IHD (418 cases) in a cohort of 12,367 male asphalt workers from Denmark, Finland, France, Germany, Israel, The Netherlands and Norway (Pope, 1989). The earliest follow up (country-specific) started in 1953 and the latest ended in 2000, averaging 17 years. Exposures to benzo(a)pyrene were assessed quantitatively using measurement-driven exposure models. Exposure to coal tar was assessed in a semi-quantitative manner on the basis of

information supplied by company representatives. A sensitivity analyses was conducted to assess potential confounding by tobacco smoking. Both cumulative and average exposure indices for benzo(a)pyrene were positively associated with mortality from IHD. The highest relative risk for fatal IHD was observed for average benzo(a)pyrene exposures of 273 ng/m or higher, for which the relative risk was 1.64 (95% confidence interval=1.13-2.38). Similar results were obtained for coal tar exposure. Sensitivity analysis indicated that even in a realistic scenario of confounding by smoking, an approximate increase of 20% to 40% excess risk in IHD in the highest PAH-exposure categories is observed. The authors concluded that these results lend support to the hypothesis that occupational PAH exposure causes fatal IHD and demonstrate a consistent exposure-response relation for this association.

3.9.3 Australian Studies

A recent study conducted in Australia examined the risk of mortality and cancer incidence with quantitative exposure to benzene-soluble fraction (BSF), benzo(a)pyrene (BaP), fluoride, and inhalable dust in two Australian prebake smelters (Sim *et al*., 2009). A total of 4,316 male smelter workers were linked to mortality and cancer incidence registries and followed from 1983 through 2002 (mean follow-up: 15.9 years, maximum: 20 years). Internal comparisons using Poisson regression were undertaken based on quantitative exposure levels. Smoking-adjusted, monotonic relationships were observed between respiratory cancer and cumulative inhalable dust exposure (trend p = 0.1), cumulative fluoride exposure (p = 0.1), and cumulative BaP exposure (p = 0.2). The exposure-response trends were stronger when examined across the exposed categories (BaP p = 0.1; inhalable dust p = 0.04). A monotonic, but not statistically significant trend was observed between cumulative BaP exposure and stomach cancer (n = 14). Bladder cancer was not associated with BaP or BSF exposure. No other cancer and no mortality outcomes were associated with these smelter exposures. The carcinogenicity of Söderberg smelter exposures is well established. The authors concluded that in these prebake smelters an association between smelter exposures and respiratory cancer, but not bladder cancer was observed. The exploratory finding for stomach cancer needs confirmation. They further commented that these results are preliminary due to the young cohort and short follow-up time

3.9.4 Effects on laboratory animals

The carcinogenic effects of exposure to PAHs by inhalation have been examined in only a few limited identified studies, all of which were restricted to BaP (Thyssen *et al* 1981; Heinrich *et al* 1986; Laskin *et al* 1970). Moreover, in two of the investigations, animals were concomitantly exposed to other compounds (Heinrich *et al* 1986; Laskin *et al* 1970). In the study by Heinrich *et al.* (1986), the incidence of lung tumours was increased in rats exposed to combustion gases of a coal furnace for an average of 16 hours/day, 5 days/week over a maximum of 22 months. The incidence of respiratory tract tumours was also increased in rats that inhaled 10ppm (103mg/m^3) BaP and the atmospheric irritant, sulfur dioxide (Laskin *et al*., 1970).

Benzo(a)pyrene has been tested in a range of species, including rats, guinea pigs, rabbits, marmosets, and rhesus monkeys. Tumours have been observed in all experiments with small animals, and the failure to induce neoplastic responses in large animals has been attributed to lack of information on the appropriate route or dose and the inability to observe the animals for a sufficient time (Osborne & Crosby, 1987). In studies with other PAHs, BaP was often used as a positive control and therefore administered at only one concentration.

BaP has been shown to be carcinogenic when given by a variety of routes, including diet, gavage, inhalation, intratracheal instillation, intraperitoneal, intravenous, subcutaneous, and intrapulmonary injection, dermal application, and transplacental administration. The carcinogenicity of individual PAH and PAH-containing mixtures in experimental animals has been well studied. Virtually no data exist on the carcinogenicity of individual PAHs in humans, although a limited database on the carcinogenicity of PAH-containing mixtures is available: these have been shown to increase the incidence of cancer in occupationally exposed human populations. The finding that a number of individual PAH are carcinogenic to experimental animals indicates that they are potentially carcinogenic to humans. PAH can produce tumours both at the site of contact and distantly, and the carcinogenic potency of PAH may vary with the route of exposure.

3.9.5 Findings of the review of the BaP health evidence

Health effects of PAHs have been reviewed extensively. Most toxic component is BaP which is a known human carcinogen. Most evidence comes from occupational studies where people have been exposed to mixtures of PAHs and animal studies. Exposure to BaP has been linked with lung cancer in a number of occupational cohorts. A recent study in Canada found a clear link between increasing BaP concentrations and the incidence of lung cancer supporting the findings of previous studies. There is evidence from recent studies that exposure to PAHs is also linked with mortality from ischemic heart disease. A recent Australian study has concluded that BaP exposure in 2 smelters is associated with respiratory cancer.

The MIL for BaP in the Air Toxics NEPM is set at 0.3ng/m^3 as an annual average. Although international air quality standards and guidelines for BaP are limited, the MIL is consistent with existing standards in the EU and New Zealand. The current national air quality standard for BaP is contained in the Air Toxics NEPM as a monitoring investigation level (MIL). The MILs are not ambient air quality standards as contained in the AAQ NEPM, but are trigger levels for further investigation and action that apply at hot-spots. If BaP is moved to the AAQ NEPM then the MIL would need to be assessed to ensure that the level of protection as a regional air quality standard is appropriate.

4. INTERNATIONAL TRENDS IN AIR QUALITY STANDARDS SINCE 1998

Air quality standards exist for the purpose of protection of human health and the environment. These standards have been developed over several decades in many countries. The review and revision of international air quality standards normally occurs via an iterative process as scientific knowledge improves, to ensure this new information is taken into account.

Many countries and other organisations have adopted air quality standards and guidelines. The World Health Organization (WHO) has been particularly influential outside the United States in the development and updating of air quality guidelines. WHO has developed and revised air quality guidelines for the protection of both human health and ecosystems since 1987. The United States Environmental Protection Agency (USEPA) adopted their air quality standards in the 1970s and is regularly reviewed. The European Union, Canada and many other countries have also developed and updated where appropriate air quality standards for the protection of human health and the environment.

When developing air quality standards, countries and jurisdictions have to consider their own specific legislative framework and policies for air quality management. Factors such as current air quality performance, trans-boundary air pollution sources and social, economic and health issues are often considered. Although frameworks and policies often differ between countries, there appears to be an international focus on attempting to harmonise approaches as far as possible. This issue has been the subject of several international conferences. Although factors such as trans-boundary air pollution do not routinely impact Australia, due to its isolation, it is important to investigate international trends in air quality standards to determine if similar considerations should be applied to the Australian context and in particular the Ambient Air Quality NEPM Standards.

In considering international trends the following organisations and countries were considered: WHO, European Union, USEPA, United Kingdom, Canada, California EPA and New Zealand. In each case, the framework for the respective standards is outlined to provide context. Revisions to standards are examined in general terms, with the primary driver for tightening a specific standard being an improved understanding of the health effects associated with exposure, based on new scientific evidence and health information. In the EU and UK, cost benefit analysis is also a central consideration in considering changes to standards.

To support these discussions and further understand the international trends in air quality standards, Tables 4.1 to 4.7 consolidates the numerical value, its form and requirements for attainment in each jurisdiction. For the purposes of this discussion paper this analysis focused on the common pollutants currently specified in the Ambient Air Quality NEPM.

4.1 Form of international standards and associated conditions

When comparing international trends, it is important to determine the form of the standard, and the differences between them. As used by the WHO and other health and environment agencies, "standards" have a specific meaning. For clarity and consistency standards need to be distinguished from guidelines.

Normally to qualify as a standard the associated criterion needs to be tightly defined. In addition to the numerical value and the averaging time the formulation of a standard

should also specify the measurement strategy, data handling procedures, and the statistics used to derive the value to be compared with the standard (WHO 1999). Standards are often legally enforceable. Conversely, guidelines are normally only advisory and provide background information and guidance to allow informed risk management decisions (WHO regional Office for Europe 2000). Although guideline values usually specify an averaging time this does not necessarily mean the measurement technique and location or statistical requirements are defined.

In Australia, the NEPM framework allows the use of standards and guidelines and their meaning and use are consistent with the approach outlined above.

The AAQ NEPM has standards (quantifiable characteristics of the environment against which environmental quality can be assessed) and protocols (procedures to be followed to determine whether the standard is being met and progress in meeting the NEPM goal). The NEPM goal is to meet the standards to a specified degree within 10 years.

The NEPC Act requires participating jurisdictions to:

- adopt any standard specified in a NEPM
- design and implement programs to meet the standard, and
- follow the standard procedure (i.e. protocols) to monitor and report achievement.

In this context, jurisdictions will be judged by their success in achieving and monitoring the environmental quality set in the NEPM. Annual reports from NEPC must be tabled in all Parliaments and is expected to ensure that all governments take their commitments seriously.

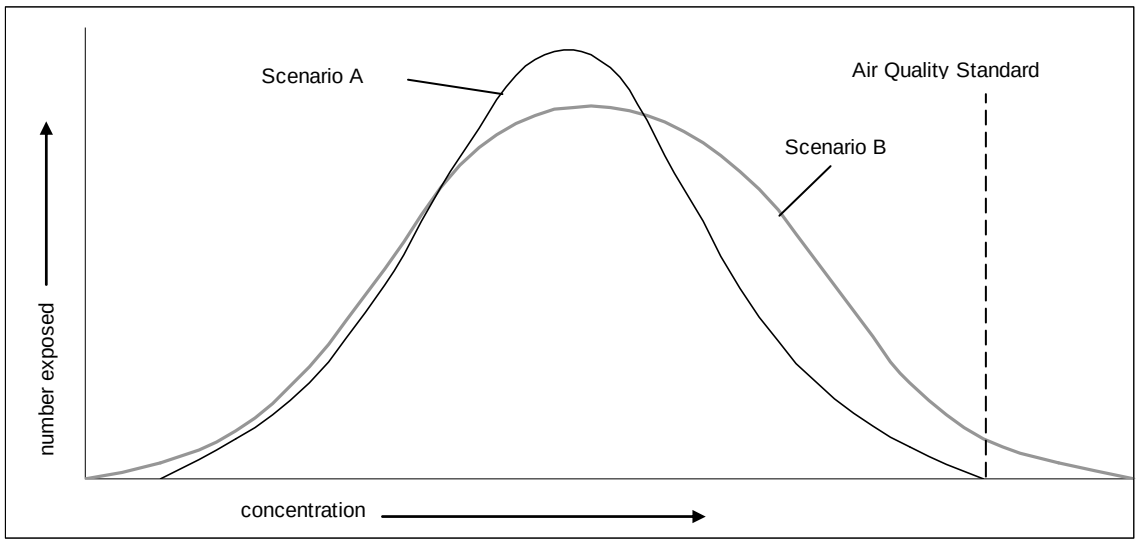
Within the NEPM framework guidelines provide direction on how specified environmental problems can be addressed or how standards or goals may be achieved. They can be part of a NEPM and set out the preferred approach to achieving or maintaining an environmental standard. This has advantages including the sharing of resources in the development of management strategies. As guidelines are not mandatory they allow jurisdictions to experiment with other approaches or for small jurisdictions to take a lower cost but, in their terms, equally effective control measure.

Internationally, the definition and legal standing of standards and guidelines are not always consistent and are often given alternative names (e.g. limit values, target values). It is also necessary to consider if the numerical values are base solely on health impacts, or whether economic and social factors are also considered. It is critical these factors are considered when comparing the numerical values specified by each international jurisdiction. These factors are considered in more detail in the following sections.

It is also important to consider the implication of allowing or not allowing exceedences of a specified numerical value. Exceedences may be permitted to allow for events that are known to occur, but can not be managed e.g. emissions from wildfires or dust storms. Alternatively, a stringent numerical value may be chosen for a particular pollutant due to the risk it poses, but allow a relatively larger number of exceedences to reflect current ambient concentrations and allows for a tightening over time to dive improvements. However, the greater the number of allowable exceedences, the higher the overall average concentration can be, leading to greater risk to the community. These risks will in part be

dependant on the magnitude of the exceedences. These concepts are presented graphically in Figure 4.1.

Figure 4.1 Potential concentration distribution with-out and with exceedences



Note: Scenario A represents the distribution of measured concentrations with-out any exceedences of the air quality standard. Scenario B represents the distribution of measured concentrations with a number of allowable exceedences of the air quality standard. Scenario B has a larger average concentration, in addition to more of the population exposed to higher concentrations. In the example given above, both of these factors increase the risk to the community.

4.2 WHO

Before discussing the WHO air quality guidelines, it is important to consider they are based solely on health considerations, unlike most air quality standards. Economic and social considerations are not taken into account when developing the guidelines and WHO recommends that these issues need to be considered when converting the guidelines to standards in individual countries.

The first WHO air quality guidelines were published in 1987. These guidelines were proposed for use in Europe. The first edition summarized scientific knowledge on the health hazards related to the 28 most common air pollutants, providing a uniform basis for risk assessment for authorities responsible for protecting populations from the adverse effects of air pollution. Since then, scientific knowledge about the effects of exposure to air pollution and the magnitude of its public health impact has increased exponentially. In the early 1990s, this growing body of knowledge allowed WHO to initiate a process for revising the guidelines, resulting in publication of the second edition air quality guidelines for Europe in 2000. These guidelines were based on health and air pollution data from Europe.

Since 2000 there has been an increasing awareness among scientists and policy-makers of the global nature and magnitude of the public health problems posed by exposure to air pollution, based on hundreds of new studies published in the scientific literature. The "Systematic review of health aspects of air pollution in Europe" carried out by the WHO to support the development of the European Union's Clean Air for Europe (CAFE) program in 2002–2004, concluded there was new evidence to warrant a revision of the air quality guidelines for particles, ozone and nitrogen dioxide (WHO Regional Office for Europe 2004).

Of particular importance in deciding that the guidelines should apply worldwide was the substantial and growing evidence of the health effects of air pollution in the low- and middle-income countries of Asia, where air pollution levels are the highest (Health Effects Institute 2004). The WHO comparative risk assessment quantified the burden of disease due to air pollution worldwide and, as noted above, found the largest burden in the developing countries of Asia (WHO 2002; WHO 2004a; WHO 2004b).

The recent review of the WHO air quality guidelines for particles, ozone, nitrogen dioxide and sulfur dioxide focussed on the globalisation of the guidelines and has considered information from various locations around the world, including Australia. The WHO states these guidelines establish the main target for air pollution levels that would be protective of health world-wide (WHO 2006).

The WHO established a steering group to manage the guideline review process. This steering group agreed on the scope and methodology of the assessment. The steering group identified experts in epidemiology, toxicology, air quality exposure assessment, air quality management and public policy, to draft the guideline document. Once the steering group had reviewed and approved the initial draft chapters they were distributed for external review to a wide group of experts in all the relevant disciplines. The WHO also sought the opinions of air quality managers and policy-makers concerning the rationale and format of the guidelines, seeking to improve their applicability in various parts of the world.

The WHO convened the Working Group on Air Quality Guidelines in Bonn, Germany, on 18–20 October 2005 to finalize the updated guidelines. The objectives of the meeting were to formulate guidelines for four specific pollutants (particles, ozone, nitrogen dioxide and sulfur dioxide) and to agree on a supporting text. The Working Group consisted of the authors of the draft chapters, the external reviewers of the drafts and members of the steering group.

In a series of plenary discussions and drafting sessions, the Working Group reviewed the general approach to the formulation of the guidelines, discussed outstanding comments from the reviewers and agreed on the general content of the background material. The drafting groups discussed in detail the formulation of the updated guidelines and the text supporting them. Final decisions concerning the recommended guidelines were arrived at in plenary by consensus.

Following the Working Group meeting, a report was prepared presenting recommendations for updated guidelines for particles, ozone, nitrogen dioxide and sulfur dioxide and summarizing the Working Group's discussions (WHO Regional office for Europe 2005). The Working Group's recommendations were reviewed and approved by the WHO and announced as updated air quality guidelines (WHO 2006).

The recent WHO review has resulted in updated guideline values for particles, ozone and sulfur dioxide (see tables 4.1 – 4.7). The WHO concluded the scientific literature has not accumulated sufficient evidence to justify revising the existing NO_2 guidelines. For particles and ozone, it is possible to derive a quantitative relationship between the concentration of the pollutant as monitored in ambient air and specific health outcomes (usually mortality). These relationships are invaluable for health impact assessment and allow insights into the mortality and morbidity burdens from current levels of air pollution, as well as the improvements in health that could be expected under different air pollution reduction scenarios.

It is worth noting that the WHO guidelines published in 2000 did not set a guideline value for PM, but instead offered guidance in the form of risk estimates (dose response relationships), as no lower adverse effects threshold was identified (WHO Regional Office for Europe 2000). This approach to no-threshold pollutants has been applied widely in risk management of environmental chemicals. Although the WHO had not formally evaluated how this guidance was used, it was suggested that it had not been well-accepted by air quality managers and policy-makers in developing countries. As a result, the updated guidelines define concentrations for the considered pollutants, which are expected to result in a significant reduction of adverse health effects. These concentrations are based on the available scientific evidence and provide an explicit objective for air quality managers and policy-makers to consider when setting national air quality standards and management strategies.

The fact that other pollutants were not included in the most recent review does not necessarily reflect a lack of new scientific evidence and health information, but the limited resources available to the project. Therefore, the previous guidelines published in 2000 for pollutants not considered in the most recent remain in effect. The steering group recommended the review of the guidelines occur as soon as possible.

4.3 European union

The European Commission has aimed to develop an overall air quality management strategy through the setting of air quality limit values, target values and long-term objectives[1]. These limit values are legally binding on all Member States of the EU. A series of Directives have been introduced to control levels of certain pollutants (CEC, 2005). The Thematic Strategy on Air Pollution (2005) proposes measures EU member countries can adopt to achieve air quality objectives established in EU legislation over the period to 2020.

[1] 'Limit value' means a level to be attained within a given period and not to be exceeded once attained. 'Target value' means a level to be attained where possible over a given period. 'Long-term objective' means a concentration to be attained in the long term.

The European Union (EU) air quality management regime started in 1980 with Directive 80/779/EEC, which set limit values and target values for SO_2 and suspended particles. In 1996, the European Commission adopted Framework Directive 96/62/EC, which aimed to establish a harmonised structure for assessing and managing ambient air quality throughout the EU. This Directive replaced previously existing legislation and introduced new air quality standards for previously unregulated air pollutants, setting the timetable for the development of daughter directives on a range of pollutants.

The Framework Directive was followed by daughter directives, which set the numerical limit values, or in the case of ozone, target values for each of the specified pollutants. The development of the daughter legislation is supported by expert working groups to prepare position papers for the European Commission as a basis to develop draft legislation. The working groups consist of technical experts from the Commission, Member States, industry and environmental NGOs and are supported as appropriate by the European Environment Agency (EEA), World Health Organisation, United Nations Economic Commission for Europe and consultants.

The first Daughter Directive (1999/30/EC) came into force in July 1999. This directive set limit values for NO_2, SO_2, Pb and PM_{10} in ambient air. The health limit values for SO_2 and PM_{10} were to be met by 2005. The other health limit values for NO_2 and Pb must be met by 2010. The second Daughter Directive (2000/69/EC) came into force on the 13 December 2000, stipulating limit values for benzene and carbon monoxide in ambient air. The third Daughter Directive related to ozone (2002/3/EC) and was required to be transposed by Member States by 9 September 2003. This third directive set a long-term objective of 120µg/m^3 (0.056ppm) (8 hour mean), which was equivalent to the then current WHO guideline value. This target value is to be met where possible by 2010.

The fourth Daughter Directive (2004/107/EC) of 15 December 2004 set limit values for air pollutants not considered by the current Ambient Air quality NEPM. This directive relates to the regulation of arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air.

The EU has often used the WHO guidelines as a starting point to develop air quality limit values incorporated into the Daughter Directives. In part, this reflects the comprehensive process the WHO follows to develop their guidelines, in addition to their past focus on European research and application. The EU assessment uses the best scientific understanding of the emissions, atmospheric transport, and human health and environmental impacts of air pollution. Where there is sufficient consensus and robust information a quantitative assessment occurs. Many health impacts have also been estimated in monetary terms. Because of this, an "Extended Cost-Benefit Analysis" has been set up, in order to include effects that are not quantified or assessed in monetary terms but are likely to be important and potentially capable of changing the balance of costs and benefits (CEC, 2005).

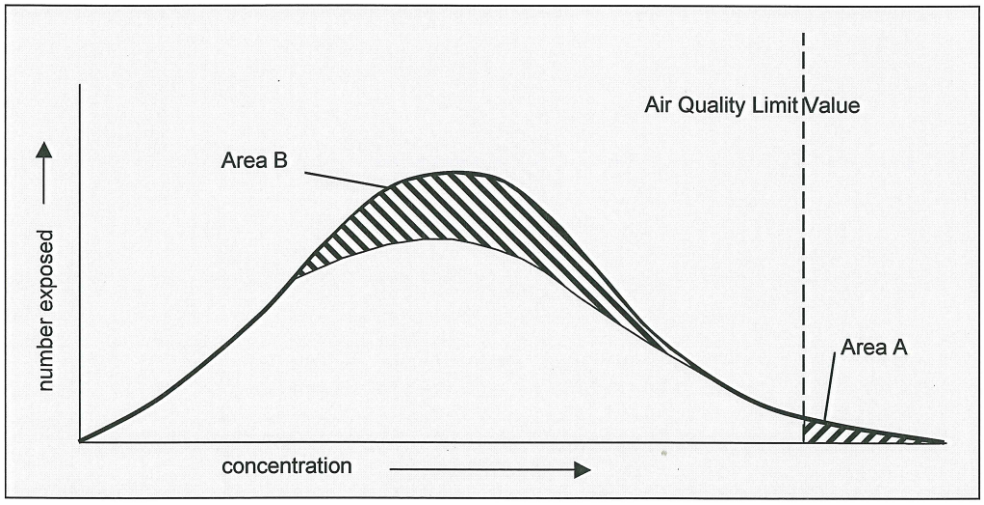
The methodology used by the EU has also been subject to independent scientific peer reviews. These reviews give details of possible uncertainties caused by model simplifications, assumptions, boundary conditions and inherent technical uncertainties. Sensitivity analyses may also be performed to assess uncertainties and the robustness of the model results, particularly uncertainties in energy demand and agricultural production, emissions data and emissions abatement factors, the various ambition levels, or target-

setting methods.

The most recent air quality related Directive (2008/50/EC) came into force on 11 June 2008. This document consolidates the existing air quality legislation (summarised above) apart from the fourth Daughter Directive, which will be brought within the new Directive at a later date. This new directive also specifies a new exposure reduction regulatory framework; and makes provision for Member States to postpone attainment deadlines and limit value obligations for certain pollutants. Under this new directive Member States are required to reduce exposure to $PM_{2.5}$ in urban areas. This is a policy direction shift from traditional compliance limits. The legislative requirement to meet air quality limit values is likely to drive Member States to focus attention on localised areas of pollution where the limits are not met. However, for pollutants such as $PM_{2.5}$, where it is widely acknowledged there is no recognised safe level for exposure this current policy framework is unlikely to generate the maximum improvement in public health for the investment made. This is because it focuses attention on localised areas only, despite much more widespread adverse effects on health being likely.

The exposure reduction approach is based on the principle that for pollutants with a low or zero threshold for adverse effects, it will generally be more beneficial to public health, and potentially more cost-effective to reduce pollutant levels across the whole population of an urban area or region rather than in a specific localised area for compliance purposes. This concept is illustrated in Figure 4.2.

Figure 4.2: Population exposure distribution



Note: Area A represents the effects of policies targeted at reducing exposure only to those exposed above the Limit Value. Area B represents the effects of policies aimed at reducing exposure in the general population. Area B is grater than Area A, and therefore, in simplified terms Policy B is more cost effective than Policy A. However, the greater level of exposure to each person in Area A will clearly need to be factored into the consideration of priority.

The EU has set an exposure reduction target of 20% by 2020 based on 2010 levels for $PM_{2.5}$. The directive obliges Member States to bring exposure levels below 20µg/m^3 by 2015. Throughout their territory Member States will need to respect the $PM_{2.5}$ limit value set at 25µg/m^3. This value must be achieved by 2015, or where possible, by 2010. The exposure is to be determined using an average exposure indicator (AEI). The AEI is assessed as a 3-

calendar year running annual mean concentration averaged over all urban background sampling sites of a Member State. The AEI for the reference year (2010) shall be the mean concentration of the years 2008, 2009 and 2010. Similarly, the AEI for the year 2020 shall be the 3-year running mean concentration averaged over all sampling points for the years 2018, 2019 and 2020.

The exposure reduction framework will focus policy on improving air quality in the places where the greatest number of people are likely to be exposed, rather than reducing high concentrations of pollution in small localised areas. This exposure-reduction framework takes into account the fact that no lower threshold for effect has been identified and that any reduction in exposure is likely to result in a health benefit to the population. The exception to this is where the AEI in the reference year is 8.5µg/m^3 or less the exposure reduction target shall be zero. The reduction target also will be zero in cases where the AEI reaches the level of 8.5µg/m^3 at any point of time during the period from 2010 to 2020 and is maintained at or below that level.

Directive (2008/50/EC) makes provision for Member States to postpone attainment deadlines and allow an exemption from the obligation to limit values for certain pollutants, subject to strict conditions and assessment by the European Commission. For example, 25 of the 27 Member States are exceeding PM_{10} limit values in at least one part of their territory. The deadlines for complying with these limits can be postponed for three years after the directive's entry into force (mid–2011). Similarly, an exemption period of five years is also available for nitrogen dioxide and benzene (2010–2015). Exemptions will be provided where relevant EU legislation such as industrial pollution prevention and control is fully implemented, and all appropriate abatement measures are being taken. The new directive provides a list of measures that need to be considered.

4.4 US EPA

As a result of air pollution's negative impacts on public health, ecosystems and the economy in the 1950s, the United States began its effort to understand air pollution problems and to develop an effective air quality management system to improve it. The federal government's first major efforts began with the *Air Pollution Control Act 1955*, which provided funds to state and local agencies for research and training.

The *Clean Air Act 1963* (CAA) and the *Air Quality Act 1967* set Air Quality Criteria, Air Quality Control Regions (AQCRs), and the process for State Implementation Plans (SIPs). This framework was further developed and refined with amendments to the CAA in 1977 and 1990. The CAA prescribes a complicated set of responsibilities and relationships among federal, states, tribal, and local agencies. The federal government coordinates efforts through the United States Environmental Protection Agency (USEPA) and sets national ambient air quality standards (NAAQS) for the common pollutants, or what it calls the "criteria" pollutants, and approaches to pollution mitigation so that an equal level of environmental protection is provided to all individuals in the US.

Two types of national air quality standards are established under the CAA. Primary standards set limits to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly. Secondary standards set limits to protect public welfare, including protection against decreased visibility, damage to animals, crops, vegetation, and buildings.

The USEPA first published NAAQS in 1971 on the basis of scientific information contained in air quality criteria (US EPA, 2006). These standards are regularly revised to critically evaluate and assess the latest scientific information published since the last revision, with the main focus being on pertinent new information useful in evaluating health and environmental effects. However, other scientific data are also discussed in order to provide a better understanding of the nature, sources, distribution, measurement, and concentrations of criteria air pollutants and their precursors in the environment.

Sections 108 and 109 of the CAA control the establishment and revision of NAAQS to provide protection for the nation's public health and the environment. The process EPA follows to review NAAQS has evolved over time. Recognizing the importance of scientific integrity and transparency, the USEPA examined the NAAQS review process. In May 2009, a number of key changes were made to the review process, this included reinstating a policy assessment document (also known as a "Staff Paper") and no longer issuing a policy assessment in the form of an Advance Notice of Proposed Rulemaking (ANPR). The major steps in the revised NAAQS review process are summarised below and provided as a flow diagram in Appendix C.

Integrated Review Plan:

The review process begins with the preparation of an integrated review plan (IRP) that includes the science-policy questions that will frame the review, an outline of the proposed process, key documents to be developed and review schedule. A workshop is held early in the planning phase to collect the Clean Air Scientific Advisory Committee (CASAC), public and other stakeholders input regarding policy-relevant questions from earlier reviews and any new policy-relevant science issues that have emerged since the last review. Based on this feedback, a draft IRP is prepared released for consultation with CASAC and the public prior to an IRP being finalised.

Integrated Science Assessment:

The integrated science assessment document (ISA) is an evaluation and synthesis of the most policy-relevant scientific studies published since the last review. First and second drafts of the ISA will be released for CASAC review and public comment. In addition, special outreach will be made to experts in other Federal agencies whose missions include assessment of health and environmental scientific information to solicit their input and comment on the science assessment.

Risk/Exposure Assessment:

A risk and exposure assessments planning document (REA) that discusses the scope and methods planned for use in conducting the assessment will be prepared in parallel with the ISA process; the first draft REA should be linked to the second draft ISA; and the second draft REA should be linked to the development of the final ISA. As with the ISA, in addition to CASAC review and public comment, special outreach will be made as appropriate to experts in other Federal agencies to solicit their input and comment on the risk/exposure assessment. The REA should include quantitative risk and exposure assessments and an assessment of the scientific evidence, including a discussion of the adequacy of the current standard and potential alternative standards. Risk and exposure assessments, focused on human health or welfare-related impacts, will

provide a concise presentation of methods, key results, observations, and related uncertainties.

Policy Assessment:

The preparation of a policy assessment (PA) document provides a transparent staff analysis of the scientific basis for alternative policy options for consideration by senior USEPA management prior to rulemaking. The PA should integrate and interpret information from the ISA and the REA to frame policy options for consideration by the USEPA Administrator. As it did in the past, this document is intended to help "bridge the gap" between the Agency's scientific assessments, presented in the ISA and REA, and the judgments required of the Administrator in determining whether it is appropriate to retain or revise the standards. This document will be released in draft form for CASAC review and public comment. The PA is intended to facilitate CASAC's advice to the USEPA and recommendations to the Administrator on any new standards or revisions to existing standards as may be appropriate, as provided for in the CAA.

Rulemaking Notices:

As required by the CAA, the USEPA will issue a proposed rule for public comment. Taking public comments into consideration, a final rule will be issued to complete the rulemaking.

The implementation of strategies for the management of air quality to meet the NAAQS is the responsibility of individual States. States must submit SIPS that set out the actions that will be taken to ensure that the NAAQS are met within a set time frame. Individual States may set their own air quality standards if they are more stringent than the NAAQS (e.g. California). The USEPA also consider the criteria pollutants as non-threshold pollutants based primarily on the inability of epidemiological studies to identify a threshold for effect.

In addition to establishing NAAQS, the USEPA also develop emission limits for industries and have adopted risk reduction approaches to the management of major sources in the US.

While individual states must prepare State Implementation Plans outlining how they will control air pollution, the US EPA takes action at a Federal level with regulations under the Clean Air Act targeting common emission sources including motor vehicles, non-road equipment, architectural coatings and consumer products.

4.5 UK

The Environment Act 1995 requires the UK Government and the devolved administrations for Scotland and Wales to produce a national air quality strategy (NAQS) containing standards, objectives and measures for improving ambient air quality. The first NAQS was adopted in 1997. This was replaced by the Air Quality Strategy for England, Scotland, Wales and Northern Ireland, published in January 2000. The most recent version of NAQS was published in July 2007 by the UK the Department for the Environment, Food and Rural Affairs (DEFRA) in partnership with the Scottish Executive, the National Assembly for Wales and the Department for the Environment for Northern Ireland. The 2007 NAQS and subsequent Air Pollution: Action in a Changing Climate (2010) identify potential new

national policy measures, supported by modelling, to help meet UK air quality standards and objectives.

The Air Quality Strategy's primary aim is to ensure that all citizens have access to ambient air without significant risk to their health, where this is economically and technically feasible. The strategy is developed on the basis that the air quality standards derived from expert recommendations represent levels at which no significant health effects would be expected in the population as a whole. The UK strategy defines:

- standards as the concentrations of pollutants in the atmosphere which can broadly be taken to achieve a certain level of environmental quality. The standards are based on assessment of the effects of each pollutant on human health including the effects on sensitive subgroups or on ecosystems
- objectives as the policy targets often expressed as a maximum ambient concentration not to be exceeded, either without exception or with a permitted number of exceedences, within a specified timescale (Department for Environment, Food and Rural Affairs 2007).

The UK standards, as the benchmarks for setting objectives, are claimed to be set purely with regard to scientific and medical evidence on the effects of the particular pollutant on health, or, in the appropriate context, on the wider environment, as minimum or zero risk levels. In the area of the effects on human health this is the approach adopted by the WHO in the formulation of their air quality guidelines and by the Expert Panel on Air Quality Standards (EPAQS) in the UK. In setting objectives derived from the health and ecosystem advice, the UK Government and the devolved administrations have also taken account of economic efficiency, practicability, technical feasibility and timescale.

When considering the UK air quality standards and objectives it should be remembered that the EU air quality limit values apply to the UK in the same way that they do to all other Member States. The UK is legally obliged to meet the EU limit values by the specified dates and to provide evidence that it has done so. Although the UK system largely mirrors that of the EU, there are some important differences. For most of the pollutants considered the numerical value and the number of permitted exceedence are identical, however the time permitted to achieve this objective is shorter under the UK system e.g. the annual average objective for NO2 was due to be met in 2005, whereas the compliance date for the EU limit value is 2010.

Another principal difference between the two systems is that the UK objectives are a statement of policy intentions or targets. As such, there is no legal requirement to meet these objectives (except in as far as these mirror any equivalent legally binding limit values in EU legislation). Local authorities are required to assess air quality against the objectives and where exceedences are thought likely, to develop action plans. However, there is no penalty if they do not meet the objectives. In the absence of absolute obligation, objectives are still set at a level at which it is thought they can reasonably be met without excessive expenditure.

4.6 Canada

Management of ambient air quality in Canada is primarily a provincial responsibility, although the Federal Government has a key mandate to carry out monitoring and research, as well as to manage air issues which have a trans-boundary or international component. The Canadian Environmental Protection Act was passed in 1988 as the principal measure for the regulation of environmental contaminants. The Federal Government can assess air

pollutants and control their impact through the setting of Canada-Wide Standards (CWS) and National Ambient Air Quality Objectives (NAAQOs) under this legislation.

Canada-wide standards (CWS) are developed for substances of national significance, through the Canada Council of Ministers of the Environment. In June 2000, the federal, provincial and territorial governments signed, with the exception of Quebec, the CWS for particles and ozone. These standards commit the government to significantly reduce particles and ground-level ozone in the ambient air by 2010. The signing of these standards was seen as an important step towards the long-term goal of minimizing the risks of these pollutants to human health and the environment in Canada. The standards selected represent a balance between the desire to achieve the best health and environmental protection possible in the relative near-term and the feasibility and costs of reducing the pollutant emissions that contribute to elevated levels of particles and ground-level ozone in ambient air.

The Canadian government's long-term air quality management goal for particles and ozone is to minimize the risks of these pollutants to human health and the environment as much as practically possible. There is clear evidence of the adverse health effects of these pollutants throughout the range of concentrations to which Canadians are exposed. This means that any reduction in the ambient levels of these pollutants provides a reduction in population health risk. This was acknowledged when the CWS were developed. The associated documentation noted there were numerous locations across Canada where ambient levels of particles and/or ozone were below the CWS levels, but still above the levels associated with observable adverse health effects. The need to ensure that jurisdictions and the broader public recognises that the CWS levels are only a first step to subsequent reductions towards the lowest observable adverse effects levels is emphasized. It goes on to say that it would be wrong to convey the impression that no action is required in these areas or that it would be acceptable to allow pollutant levels to rise to the CWS levels. Jurisdictions should take remedial and preventative actions to reduce emissions from anthropogenic sources in these areas to the maximum extent practicable (CCME 2000).

NAAQOs establish a national goal for ambient air quality that protects public health, the environment, or aesthetic properties of the environment. It is primarily effects-based but also considers technological, economic and social information. It represents the air quality management goal for the protection of the general public and the environment of Canada.

Up until 1998, Canada had a three-tiered system of NAAQOs. However, this tiered system has been replaced. The current framework establishes a single level. NAAQOs are established and reviewed based on recommendations from the Working Group on Air Quality Objectives and Guidelines (WGAQOG) which report to the Canadian Environmental Protection Act -National Advisory Committee. The WGAQOG consists of representatives of federal, provincial and territorial departments of environment and health.

Provincial governments can adopt NAAQOs through a process of their choice, implementing them as they see fit (e.g. local source permitting, for air quality index and as benchmarks for developing provincial objectives and standards). Individual provinces are also able to develop additional or more stringent air quality objectives or guidelines, if deemed necessary for environmental management in their particular jurisdiction.

The Canadian Government announced a new regulatory framework for air and greenhouse emissions and its Turning the Corner Action Plan in 2007, which foreshadowed regulation

of a number of product sectors and mandatory emissions reductions by industry. A key component will be a national Clean Air Act (still to be enacted) which will strengthen the Federal government's ability to take action to reduce air (and greenhouse) emissions.

4.7 California EPA

Although the Federal Clean Air Act requires the USEPA to set ambient air quality standards for the nation, it also permits individual States to adopt additional or more protective air quality standards. California law authorizes the California Air Resources Board (CARB) to set ambient air quality standards (California Health and Safety Code section 39606). California has set standards for certain pollutants, such as particulate matter and ozone, which are more protective of public health than respective federal standards. California has also set standards for some pollutants that are not addressed by federal standards.

In California ambient air quality standards are said to define clean air and are established to protect even the most sensitive individuals in its communities. An air quality standard defines the maximum amount of a pollutant that can be present in outdoor air without harm to the public's health. Economic and social factors are not considered as part of the standard development process, nor are the timeframes for compliance. These factors and associated costs are assessed when management actions are being considered

Children have been identified as a vulnerable group that must be considered when developing air quality standards. The *Children's Environmental Health Protection Act (CEHPA, California Senate Bill 25, Escutia, 1999)* required CARB and Office of Environmental Health Hazard Assessment to evaluate all ambient air quality standards by December 2000 to determine whether these standards adequately protect human health, particularly that of infants and children. The CEHPA also required staff to prioritize those standards found to be inadequate for full review and possible revision. The evaluation found that health effects may occur in infants, children, and other potentially susceptible groups exposed to pollutants at levels near several of the standards, with particles (PM_{10}), ground-level ozone and nitrogen dioxide receiving the highest priority for review and possible revision.

In June of 2002, staff completed a review of published studies on the health effects of particles and sulfates, the highest priority pollutants. The CARB adopted staff recommendations to revise the PM_{10} standard, establish a new $PM_{2.5}$ annual standard and retain the existing sulfates standard. Staff also reviewed the published scientific literature on ground-level ozone and nitrogen dioxide. On 28 April 2005, CARB approved staff recommendations to retain the existing 1-hour ozone standard of 0.09ppm, and establish a new 8-hour standard of 0.070ppm. Subsequently, on 22 February 2007, CARB approved staff recommendations to amend the NO_2 standard by lowering the existing 1-hour-average standard for nitrogen dioxide to 0.18ppm, not to be exceeded; and establishing a new annual average standard for nitrogen dioxide at 0.030ppm, not to be exceeded. CARB provide no guidance as to when the standards should be achieved.

Over time, the lower priority ambient air quality standards will be reviewed as well. Regulations also require the review of standards whenever substantial new information pertaining to ambient air quality standards becomes available, or at least once every five years.

4.8 New Zealand

New Zealand's national environmental standards are mandatory technical environmental regulations. They have been developed under the Resource Management Act 1991 and are encapsulated within the Resource Management (National Environmental Standards Relating to Certain Air Pollutants, Dioxins and Other Toxics) Regulations 2004. These standards have the force of regulation as a result.

In October 2004, five ambient air quality standards were introduced, these being for carbon monoxide, fine particles (PM_{10}), nitrogen dioxide, sulfur dioxide and ozone.

In August 2005, the definition of an airshed was amended so that all regions of New Zealand are airsheds and the ambient standards as a result now apply everywhere. The regulations place a requirement on regional councils to monitor air quality and to report exceedences to the public. It is well known that a number of urban areas do not meet the ambient standard for particles. Whilst not a statutory requirement, councils are encouraged to develop airshed action plans to assist them in achieving compliance with the standard by 2013.

The ambient standards are based upon the existing Ambient Air Quality Guidelines (MfE, 2002). These guidelines were developed following a comprehensive review of international and national research, and are widely accepted amongst New Zealand practitioners. It is important to understand how the standards and guidelines fit together in the regulatory framework.

The Ambient Air Quality Guidelines were published by the Ministry for the Environment as guidance under the RMA. They provide the minimum requirements that outdoor air quality should meet in order to protect human health and the environment. Guideline levels for pollutants (and averaging periods) not covered by the standards still apply. The standards replace any previous guideline levels for that particular pollutant and averaging period.

Where air pollution levels breach guideline values, emission reduction strategies should be implemented to improve air quality. Where levels do not breach the values, efforts should be made to maintain air quality and, if possible, reduce emissions. These recommendations still apply to pollutants not included within the standards. The primary purpose of the standards is to provide a guaranteed level of protection for the health of all New Zealanders. The ambient standards are seen as the minimum requirements that air quality should meet in order to guarantee a set level of protection for human health and the environment and override any less stringent requirements in regional plans.

4.9 Conclusions

All the international air quality standards (or guidelines/objectives) considered in this discussion document are based on extensive scientific evidence, which concludes health effects occur as a result of exposure. Although this information has gaps and uncertainties within the data, the literature provides a strong foundation for the development of the final numerical values. A number of key findings in relation to air quality standards have been highlighted by the international literature. There appears to be an increasing acceptance by the international jurisdictions considered, that many of the criteria pollutants, based on the results of epidemiological studies, have no identified threshold below which adverse health effects are not observed; and therefore any standards will have some level of risk associated

with them. This has led some international agencies to adopt an 'exposure—reduction' or 'risk—reduction' approach to air quality management. In these approaches the attainment of the standards is considered as a minimum target.

Epidemiological research, particularly for ozone and particles implies that a numerical standard cannot provide complete protection for the entire population since no lower adverse effects level threshold has been identified. This is supported by the fact that ozone and PM concentrations currently found in many cities in developed countries continue to present risks to health. There is also an increasing range of adverse health effects being linked to air pollution, with many of these at low pollutant concentrations. This is especially true for particles. New studies use more refined methods and more subtle but sensitive indicators of effects such as physiological measures (e.g. changes in lung function, inflammation markers). Decisions are required to determine what constitutes an adverse health effect. The EPHC Standards Setting Working Group is developing guidance on this important issue.

As our understanding of air pollution mixtures in the atmosphere improves, the implications of attempting to monitor and manage these mixtures via a single air pollutant standard have become increasing apparent. An example of this is nitrogen dioxide, which is a product of combustion and is generally found in the atmosphere in close association with other primary pollutants, including ultrafine particles. It is also a precursor of ozone and therefore co-exists in photochemically generated oxidant pollution. Nitrogen dioxide is itself toxic, and its concentrations are often strongly correlated with those of other toxic pollutants. As nitrogen dioxide is easier to measure, it is often used as a surrogate for the mixture as a whole. Achieving the standard or guideline for individual pollutants such as nitrogen dioxide may therefore bring benefits for public health that exceed those anticipated based on estimates of the pollutant's specific toxicity.

The information provided in Table 4.1 to Table 4.7 summarises the standards/guidelines that have been adopted internationally for the criteria pollutants. Although there is some consistency in the numerical values how the standards apply can vary considerably. The form of the standard—where compliance is assessed, number of allowable exceedences, percentile form of the standard etc—impact significantly on the level of health protection inherent in the meeting of the standard.

In the US the approach to assessing compliance with the standards and the form of the standard varies with each pollutant. For $PM_{2.5}$ compliance with standard is assessed as the 3 year average of 98th percentile values. This approach is taken to provide a more stable guide for air quality management purposes. This approach leads to a different number of exceedences of the standard depending on the existing air quality. This means that there is no consistency in the level of risk experienced across different locations. Compliance is assessed at the population oriented monitor that reads the highest value within an area. Data from peak sites are not included in the assessment as to whether there is a violation of the standard.

In assessing compliance the USEPA have both an exceptional events and a natural events policy that enables the removal of unusual events from the dataset when assessing whether an area is in compliance or not with the standard. The natural events rule applies to severe events such as volcanic or seismic activity, wildfires and dust storms. In addition to these events the exceptional events rule also includes events such as high winds, sandblasting, structural fires, chemical spills and industrial accidents, high pollen counts, construction

and demolition, highway construction, agricultural tilling, unusual traffic congestion, prescribed burning, clean up activities after a major disaster, plus several others. There are strict guidelines for the identification, flagging and reporting of the data and the rules only apply in the assessment of whether an area is in violation of the air quality standards.

For assessing compliance with the $PM_{10,}$ the standard is not to be exceeded more than once per year on average over 3 years. This means that one year could have more exceedences if the other 2 years did not have any. For ozone compliance is assessed differently for the 8-hour and 1-hour standards (note that the 1-hour standard only applies in areas where the 8-hour standard is expected to be exceeded). Compliance with the 8-hr standard is achieved when the 3 year average of the 4^{th} highest daily maximum measured at each monitor does not exceed standard. For the 1-hr standard an area is considered in compliance if standard exceeded no more than 1 day/year. For both CO and SO_2 the standards are not to be exceeded more than once per year. As the standard for NO_2 is an annual mean no exceedences are associated with the standard.

The Californian standards are not to be exceeded standards. Although many areas in California are not in compliance with these standards any exceedence of the standards is considered a violation of the standard. There are no allowable exceedences associated with these standards. The UK objectives are not legally binding but are used to drive improvements in air quality. The standards are derived based solely on health considerations. The objectives established in the air quality strategy set timeframe and number of exceedences. The number of allowable exceedences is based on consideration of social, technological and environmental issues. The number of allowable exceedences varies with each pollutant. The EU limit values are legally binding on UK.

In interpreting the information in the following tables it is important to consider the differences in how the standards apply and the number of allowable exceedences both of which can impact significantly on the level of health protection associated with the meeting of a standard. For example, meeting a 'not to be exceeded standard' of 50µg/m^3 for PM_{10} provides a far greater level of health protection than the meeting of the same numerical value with 35 allowable exceedences.

Table 4.1 Australian and selected international air quality criteria for CO

Jurisdiction	Numerical values (averaging time)				Attainment and allowable exceedances				Form of standard	Date to achieve by
	15 minutes	30 minutes	1 hour	8 hours	15 minutes	30 minutes	1 hour	8 hours		
WHO	100mg/m^3 (80ppm)	60mg/m^3 (48ppm)	30mg/m^3 (24ppm)	10mg/m^3 (8ppm)	-	-	-	-	Guideline	-
European Union				10mg/m^3 (8ppm)	-	-	-	-	Standard	1 Jan 2005
US EPA			35ppm	9ppm			1 exceedence/year	1 exceedence/year	Standard	
UK				10mg/m^3 (8ppm)				-	Objective (Standard)	31 Dec 2003
Canada										
California EPA			20ppm	9ppm			-	-	Standard	-
New Zealand				10mg/m^3 (8ppm) (running mean)				1 exceedence/year	Standard	1 Sept 2005
Australia[1]				9ppm				1 day/year	Standard	8 July 2008

Note:

[1] Although the AAQ NEPM was made by NEPC on 26 June 1998, it did not become a legal policy instrument until it was gazetted. The gazettal date was 8 July 1998.

Table 4.2 Australian and selected international air quality criteria for NO_2

Jurisdiction	Numerical values (averaging time)		Attainment and allowable exceedances		Form of standard	Date to achieve by
	1 hour	Annual	1 hour	Annual		
WHO	200µg/m³ (0.097ppm)	40µg/m³ (0.019ppm)	-		Guideline	-
European Union	200µg/m³ (0. 097ppm)	40µg/m³ (0.019ppm)	18 exceedences/year;	-	Standard	1 Jan 2010
US EPA	20.5µg/m³ (0.10ppm)	0.053ppm (arithmetic)		-	Standard 98 percentile 3 year daily max 1-hr values	
UK	200µg/m³ (0. 097ppm)	40µg/m³ (0.019ppm)	18 exceedences/year;	-	Objective (Standard)	31 Dec 2005
Canada						
California EPA	0.18ppm	0.030ppm			Standard	-
New Zealand	200µg/m³ (0. 097ppm)		9 exceedences/year		Standard	1 Sept 2005
Australia	0.12ppm	0.03ppm	1 day/year	-		8 July 2008

Table 4.3 Australian and selected international air quality criteria for Ozone

Jurisdiction	Numerical values (averaging time)			Attainment and allowable exceedances			Form of standard	Date to achieve by
	1 hour	4 hours	8 hours	1 hour	4 hours	8 hours		
WHO			100µg/m^3 (0.047ppm)			-	Guideline	-
European Union			120µg/m^3 (0.056ppm)			25 days averaged over 3 years	Objective	31 Dec 2010
US EPA[1]	0.12ppm		0.075ppm	1 day/year		Achievement to be based on the 4th highest measurement annually, averaged over 3 consecutive years.	Standard	
UK			100µg/m^3 (0.047ppm)			10 exceedences/year	Objective (Standard)	31 Dec 2005
Canada			0.065ppm			Achievement to be based on the 4th highest measurement annually, averaged over 3 consecutive years.	Standard	2010
California EPA	0.09ppm		0.07ppm	-		-	Standard	-
New Zealand	150µg/m^3 (0.08ppm)			-			Standard	1 Sept 2005
Australia	0.10ppm	0.08ppm			1 day/year	1 day/year	Standard	8 July 2008

Note:

[1] The US EPA 1 hour ozone standard only applies to specific areas. As of June 15, 2005 EPA revoked the 1-hour ozone standard in all areas except the 8-hour ozone non-attainment Early Action Compact (EAC) Areas. Proposing new 8 hr standard of 0.06 to 0.07 ppm.

Table 4.4 Australian and selected international air quality criteria for SO_2

Jurisdiction	Numerical values (averaging time)					Attainment and allowable exceedances					Form of standard	Date to achieve by
	10 minutes	15 minutes	1 hour	24 hours	Annual	10 minutes	15 minutes	1 hour	24 hours	Annual		
WHO	500µg/m³ (0.175ppm)			20µg/m³ (0.007ppm)		-			-		Guideline	-
European Union			350µg/m³ (0.122ppm)	125µg/m³ (0.044ppm)				24 exceedences/ year	3 exceedences/ year		Standard	1 Jan 2005
US EPA (sulfur oxides)				0.14ppm	0.03ppm (arithmetic)				1 exceedences/ year	-	Standard	
UK		266µg/m³ [A] (0.093ppm)	350µg/m³ (0.122ppm)[B]	125µg/m³ (0.044ppm)			35 exceedences/ year	24 exceedences/year	3 exceedences/ year		Objective (Standard)	[A] 31 Dec 2005 [B] 31 Dec 2004
Canada												
California EPA			0.25ppm	0.04ppm				-	-		Standard	-
New Zealand			(a) 570µg/m³ (0.199ppm) (b) 350µg/m³ (0.122ppm)					(a) - (b) 9 exceedences/ year			Standard	1 Sept 2005
Australia			0.20ppm	0.08ppm	0.02ppm			1 day/year	1 day/year	-	standard	8 July 2008

USEPA currently reviewing SO_2 standards. Propose to revoke 24 hr and annual average standards and introduce new 1 hour average between 0.05 to 0.1 ppm (4th highest of 3 year average)

Table 4.5 Australian and selected international air quality criteria for Lead

Jurisdiction	Numerical values (averaging time)			Attainment and allowable exceedances			Form of standard	Date to achieve by
	30 days	Quarterly	Annual	30 days	Quarterly	Annual		
WHO			0.5µg/m^3			-	Guideline	-
European Union			0.5µg/m^3			-	Standard	1 Jan 2005
US EPA		0.15µg/m^3			-		Standard	
UK			0.25µg/m^3			-	Objective (Standard)	31 Dec 2008
Canada								
California EPA	1.5µg/m^3			-			Standard	-
New Zealand								
Australia			0.5µg/m^3			-		8 July 2008

Table 4.6 Australian and selected international air quality criteria for PM_{10}

Particles (PM_{10})						
Jurisdiction	**Numerical values (averaging time)**		**Attainment and allowable exceedances**		**Form of standard**	**Date to achieve by**
	24 hours	**Annual**	**24 hours**	**Annual**		
WHO[1]	50µg/m³	20µg/m³	-	-	Guideline	-
European Union	50µg/m³	40µg/m³	35 exceedences/year	-	Standard	1 Jan 2005
US EPA	150µg/m³		1 exceedence/year on average over a 3 year period		Standard	
UK	50µg/m³	40µg/m³	35 exceedences/year-	-	Objective (Standard)	31 Dec 2004
Canada						
California EPA	50µg/m³	20µg/m³ (arithmetic)	-	-	Standard	-
New Zealand	50µg/m³		1 exceedence/year		Standard	1 Sept 2005
Australia	50µg/m³		5 days /year		Standard	8 July 2008

Note:

[1] The $PM_{2.5}$ guideline value are converted to the corresponding PM_{10} guideline value by application of a $PM_{2.5}/PM_{10}$ ratio of 0.5. This ratio is typical of developing country urban areas and is at the bottom of the range found in developed country urban areas.

Table 4.7 Australian and selected international air quality criteria for $PM_{2.5}$

Jurisdiction	Numerical values (averaging time)		Attainment and allowable exceedances		Form of standard	Date to achieve by
	24 hours	Annual	24 hours	Annual		
WHO	25µg/m³	10µg/m³	-	-	Guideline	-
European Union		25µg/m³		-	target	2010
US EPA	35µg/m³	15.0µg/m³ (arithmetic)	Attainment based on the 3-year average of the 98th percentile of 24-hour concentrations at each population-oriented monitoring site .	Attainment based on the 3-year average of the weighted annual mean concentrations from single or multiple community-oriented monitoring sites.	Standard	
UK		25µg/m³		-	Objective (Standard)	2020
Canada	30µg/m³		Attainment based on the 98th percentile ambient measurement annually averaged over 3 consecutive years.		Standard	2010
California EPA		12µg/m³ (arithmetic)		-	Standard	-
New Zealand						
Australia[1]	25µg/m³	8µg/m³	-	-	Advisory reporting standard	-

Notes:

[1] Goal is to gather sufficient data nationally to facilitate a review of the Advisory Reporting Standards as part of the review of this measure.

5. ISSUES TO BE CONSIDERED IN EVALUATION OF NEPM STANDARDS

As discussed in the previous sections there has been a significant amount of new evidence, both internationally and in Australia, about the health of effects of the common (criteria) pollutants since the AAQ NEPM was made in 1998. The studies conducted in Australia indicate that the health effects observed overseas are also observed here even though air quality in Australian cities is generally much better than that experienced in similar sized cities elsewhere.

As discussed in Section 2, the standards contained in the AAQ NEPM were based on the understanding, of the health effects of these air pollutants, which existed at the time of making the NEPM. The form of the standards—setting a timeframe for compliance and an allowable number of exceedences (the goal associated with the standards)—was adopted on the basis of an understanding of the achievability of those standards within 10 years of making the NEPM. There was limited information available to inform that decision at the time of making the NEPM.

However, the AAQ NEPM has been a positive step forward in the management and assessment of air quality in Australia. The NEPM has provided a nationally consistent framework for the monitoring and reporting of air quality and has provided the incentive for increased monitoring of air quality in smaller jurisdictions and has also promoted increased monitoring of particles—both PM_{10} and $PM_{2.5}$ nationally. The air quality standards contained in the NEPM have provided nationally consistent benchmarks against which the quality of our air and the risk posed by air pollution to the Australian population can be assessed. The implementation of the NEPM by jurisdictions has led to greater consistency in air pollution data and a much stronger database to enable an assessment of the achievability of any new standards that may be developed.

One important aspect of these data, including data for PM_{10} and $PM_{2.5}$, is that the results of epidemiological studies worldwide are indicating that there is no threshold for the health effects associated with exposure to these pollutants. As discussed in Section 4 this information has led to changes in air quality standards for these pollutants internationally. For the non-threshold pollutants the standards (in Australia and overseas) have been adopted with acknowledgement that there is a level of residual risk associated with those standards.

Another important consideration for the review of the AAQ NEPM is whether the current form of the standard which provides for an allowable number of exceedences is still appropriate. The information provided in Section 4 highlights the variability worldwide in the form of the standards adopted, how compliance is assessed and allowable number of exceedences. This variability leads to significant differences in the level of protection offered by the standards in different locations even if the numerical value of the standard is the same. The greater the number of allowable exceedences, the less protective of human health is the standard.

Therefore on the basis of the information provided in the previous sections there is a number of issues that need to be considered in the evaluation of whether the current standards are still appropriate:

- Is there sufficient new health evidence to support a revised standard and if so, for which pollutants?
- Does the current approach, which allows for a number of exceedences of the standard, meet the requirement for adequate protection or are there alternative methods that could provide more consistency in the level of health protection associated with complying with the NEPM standards?
- Should changes be made to the reporting protocols that would lead to a greater transparency and better understanding of the causes of exceedences in jurisdictions, the potential risk to population health, and management approaches being undertaken to address these exceedences?
- See discussion on these issues below and your opinion on the alternatives is sought.

As discussed previously there is a large body of information worldwide that identifies that there are health effects associated with exposure to air pollution at levels below the current NEPM standards. The studies commissioned by EPHC to inform this review show that even at levels currently experienced in Australian Cities, there are strong associations between exposure to NO_2, PM_{10}, $PM_{2.5}$, CO and SO_2 and increases in daily mortality and hospital admissions for respiratory and cardiovascular causes. Given that these pollutants are considered as 'non-threshold' pollutants, there will always be some level of risk associated with the standard at whatever numerical value is set.

The question that arises is whether this new evidence is sufficient to require evaluation through the application of the risk assessment methodology developed by the SSWG for the setting of air quality standards. If so, the application of this methodology would allow an assessment to be made of whether any changes are required to the current standards to ensure that adequate protection of the Australian population is achieved through the meeting of the standards. The application of the SSWG methodology would occur through a Variation process for the NEPM if such a process is considered necessary.

The alternative is to maintain the current standards without further evaluation as to whether any change may be required. However, this would mean that the standards in the NEPM would not reflect the current understanding of the health effects of these pollutants, in particular the results of studies that have been conducted in Australia. Therefore meeting the standards may not provide adequate protection for the Australian population of the adverse health effects of air pollution.

Is there sufficient evidence to support a recommendation to NEPC to revise the current standards in a variation to the NEPM? If so, for which pollutants?

The current goal associated with the NEPM standards sets an allowable number of exceedences that was to be met within 10 years of the making of the NEPM. The number of exceedences was determined by an evaluation of the achievability of meeting the standard within that 10 year timeframe. As discussed previously the NEPM standards were developed to protect the Australian population from adverse health effects associated with exposure to these pollutants if jurisdictions managed air quality to ensure that these standards were met. As there appears to be a linear relationship between exposure to these pollutants and adverse health effects any increase in air pollution levels will lead to an increase in risk to the health of the population. In other words, setting allowable number of exceedences leads to an effective weakening of the level of protection associated with the standards.

As discussed in section 4, there are a number of approaches used internationally to assess compliance and taking into account the costs and benefits associated with achieving the standards. These include:

- including an allowable number of exceedences
- assessing compliance with the standard using a percentile form (not specifying an allowable number of exceedences)
- having a 'not to be exceeded' standard based on health protection and requiring reporting of cause of exceedences, progress toward meeting the standards and actions taken (the reporting alternative is discussed further in the next section)
- enabling 'exceptional' or 'natural' events to be excluded from the assessment of whether the air quality in a region is in compliance with the standards or not.

The implication of setting an allowable number of exceedences is discussed above. The use of a percentile form, such as the approach used in the US for $PM_{2.5}$ and PM_{10}, also allows exceedences of the standards to occur but is not explicit is setting a limit for these exceedences. As discussed in section 4 this approach allows variability in the number of exceedences experienced in areas of differing air pollution levels. This approach may not deliver the requirement of the NEPC Act for 'equivalent protection for all Australians' or achieve the national consistency that the NEPM has been designed to achieve.

The use of 'not-to-be-exceeded' standards provides a target for air quality management while ensuring that the basis for the standards is still clearly health based with the level of protection associated with the standard defined. The achievability of meeting the standards is assessed either through setting a timeframe for the meeting of the standard or requiring jurisdictions to assess the timeframe for compliance and developing air quality management strategies that will deliver the required improvements in air quality to meet the standards. The transparency and accountability in meeting the standards comes through clear and well defined reporting processes (as discussed below).

Does the current approach, which allows for a number of exceedences of the standard, meet the requirement for 'adequate protection' or are there alternative methods that could provide more consistency in the level of health protection associated with complying with the NEPM standards?

The impact of climate change is predicted to have a significant impact on air quality in the future and will provide challenges to all jurisdictions in meeting air quality standards, in particular those for particles and ozone. The frequency and severity of bushfires and dust storms are predicted to increase. These events are known to significantly increase both PM_{10} and $PM_{2.5}$ levels across both urban and rural areas of Australia. Rural communities in many parts of Australia are already being impacted by increased dust levels due to prolonged periods of drought. This is likely to increase as the impacts of climate change become more apparent across Australia. How do we take this into account in the setting of air quality standards while still ensuring that in meeting the standards that the health of the Australian population is protected? One option is to include provisions within the NEPM for 'natural' or 'exceptional' events to be excluded from assessing whether the air quality standards have been met or not. This approach is used in the US and focuses assessment of compliance on air pollution that can be managed through the implementation of management strategies and policies to improve air quality. There is strict guidance on how these events are identified and this must be reported. Air pollution data arising from these events is not

excluded from air quality databases or from public reporting. It is only taken into account when assessing whether an area is in compliance with the standards or not. Such an approach would overcome the arbitrary setting of an 'allowable' number of exceedences for these standards (as is currently the case for PM_{10}) while focussing actions for improvement in air quality on areas where clear and well defined management strategies can be developed.

The standards for $PM_{2.5}$ in the AAQ NEPM are advisory reporting standards. There is no timeframe set for compliance with these standards or an allowable number of exceedences. The incorporation of advisory reporting standards in the NEPM was to ensure that jurisdictions collected sufficient data on $PM_{2.5}$ to enable the setting of 'compliance' standards through this review process while setting a clearly defined health based target for the development of air quality management strategies. The advisory reporting standards are treated differently across jurisdictions and by key stakeholders. This is an issue for consideration in this review process. There is strong health evidence that $PM_{2.5}$ poses a significant risk to human health and this remains a key driver for consideration of the need for compliance standards for this pollutant.

The reporting of air quality against the NEPM standards is the key mechanism for jurisdictional accountability for the implementation of the NEPM requirements. As discussed in previous sections, the numerical value and form of the standard only go part of the way in informing communities about whether air quality in their region meets the health based standards and allowable number of exceedences or not. The current reporting protocol requires assessment against these benchmarks and identification of what has led to any non-compliance. There is no strict guidance on or requirement to assess and provide clear justification for sources of exceedences.

If the standards in the NEPM were to change to a not-to-be exceeded form, or a natural events approach was adopted to account for the impact fires and dust on air quality, then achievability issues could be defined and addressed through the reporting protocols. For example, jurisdictions could be required to assess the timeframe required to meet the standards and identify management actions that they would implement to ensure that air quality met the standards within that time period. Annual reporting would include progress against these goals. Strict guidance for the assessment and reporting could be developed and included as a schedule to the NEPM.

The inclusion of a natural events rule would enable identification of issues that impact on air quality to be separated into 'natural' events that are not easily managed and 'anthropogenic' impacts that are manageable through the implementation of air quality management strategies. Strict guidance would need to be provided to identify what constitutes a 'natural' event (similar to the guidance developed by the USEPA) to ensure national consistency. The justification and analysis would need to be included in the annual reporting to NEPC.

Inclusion of a stricter reporting protocol and analysis of air quality issues would go part of the way to enabling a more transparent approach to implementation of health based standards than the current situation that has an allowable number of exceedences that effectively weaken the standard.

Are there changes that could be made to the reporting protocols that would lead to a greater transparency and better understanding of the causes of exceedences in jurisdictions and

management approaches being undertaken to address these exceedences and potential risk to population health?

6. WHERE TO FROM HERE

6.1 The next steps

This Discussion Paper (the second of two discussion papers developed during the review) provides background on the basis used to derive the NEPM standards in Australia, the selection of health outcomes on which the standards were focussed, and the form of the current standards. It then reviews and examines new Australian and international knowledge of the effects of air pollution on human health and the international response to this new information. The Paper then discusses the alternative proposals in response to the new health evidence that may influence the current standards and their form.

Four advisory groups have been formed to assist NEPC in the review of the NEPM - the Non-government Organisations Advisory Group (NGO), the Jurisdictional Reference Network (JRN), the Health Advisory Group (HAG) and the Technical Advisory Group (TAG). These groups have provided input to the development of the discussion papers.

Stakeholder input is being sought and comments are invited on the information presented, the issues raised and the proposed options. The feedback provided will be used to inform any recommendations made to NEPC about the need to vary any aspects of the AAQ NEPM.

Once consultation on this Discussion Paper is completed a report will be prepared for consideration by NEPC that will identify whether aspects of the NEPM need to be varied and the options to vary the NEPM. It is anticipated that the review recommendations will be finalised for consideration by NEPC in November 2010.

The final step prior to varying the NEPM (if required) will involve the preparation of a draft varied NEPM and an Impact Statement (as required by Section 20 of the NEPC Act). The Impact Statement must include an assessment of environmental, economic and social impacts. In accordance with the NEPC Acts and the NEPC Consultation Protocol, both the draft variation and the Impact Statement must be made available for public consultation. NEPC must have regard to the Impact Statement and submissions received during the consultation period in deciding whether to adopt a proposed variation to the NEPM.

6.2 Submissions

This discussion paper is available on the EPHC website <www.ephc.gov.au> for comment for a period of six weeks. No formal response will be provided on submissions to the discussion paper. All submissions will be considered public documents unless clearly marked "confidential" and may be made available to other interested parties, subject to Freedom of Information Act provisions.

Submissions should be received by the NEPC Service Corporation by close of business ***Friday 27 August 2010***. To allow ease of photocopying, hardcopy submissions should be unbound. Electronic submissions should preferably be provided as a Word for Windows file.

Submissions may be made by:

email to kscott@ephc.gov.au

CD Rom, or in hardcopy to:

Ms Kerry Scott, Project Manager, NEPC Service Corporation, Level 5/81 Flinders Street

ADELAIDE SA 5000

7. GLOSSARY

(Including terms and descriptions from IPCS harmonisation project)

Term	Description
Acceptable daily intake	Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub population may be exposed daily over their lifetime without appreciable health risk. Related terms: Reference dose, Tolerable daily intake
Acceptable risk	A risk management term. The acceptability of the risk depends on scientific data, social, economic, and political factors, and the perceived benefits arising from exposure to an agent.
Adverse effect	Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Analysis	Detailed examination of anything complex, made in order to understand its nature or to determine its essential features.
Assessment	Evaluation or appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.
Assessment end-point	Quantitative/qualitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.
Assessment factor	Numerical adjustment used to extrapolate from experimentally determined (dose–response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: Safety factor, Uncertainty factor
Concentration	Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.
Concentration–effect relationship	Relationship between the exposure, expressed in concentration, of a given organism, system, or (sub) population to an agent in a specific pattern during a given time and the magnitude of a continuously graded effect to that organism, system, or (sub) population. Related terms: Effect assessment, Dose–response relationship
Dose 1	Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population.
Dose–effect relationship	Relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population and the magnitude of a continuously graded effect to that organism, system, or (sub) population. Related terms: Dose–response relationship, Effect assessment, Concentration–effect relationship
Dose-related effect	Any effect to an organism, system, or (sub) population as a result of the quantity of an agent administered to, taken up by, or absorbed by that organism, system, or (sub) population.

Term	Description
Dose–response	Relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population and the change developed in that organism, system, or (sub)population in reaction to the agent. Synonymous with Dose–response relationship. Related terms: Dose–effect relationship, Effect assessment, Concentration–effect relationship
Dose–response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment. Related terms: Hazard characterization, Dose–effect relationship, Effect assessment, Dose–response relationship, Concentration–effect relationship
Dose–response curve	Graphical presentation of a dose–response relationship.
Dose–response relationship	Relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population and the change developed in that organism, system, or (sub) population in reaction to the agent. Related terms: Dose–effect relationship, Effect assessment, Concentration–effect relationship
Effect	Change in the state or dynamics of an organism, system, or (sub) population caused by the exposure to an agent.
Effect assessment	Combination of analysis and inference of possible consequences of the exposure to a particular agent based on knowledge of the dose–effect relationship associated with that agent in a specific target organism, system, or (sub) population.
Expert judgment	Opinion of an authoritative person on a particular subject.
Exposure 1	Concentration or amount of a particular agent that reaches a target organism, system, or (sub) population in a specific frequency for a defined duration.
Exposure assessment 1	Evaluation of the exposure of an organism, system, or (sub) population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.
Exposure scenario 1	A set of conditions or assumptions about sources, exposure pathways, amounts or concentrations of agent(s)involved, and exposed organism, system, or (sub) population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.
Fate	Pattern of distribution of an agent, its derivatives, or metabolites in an organism, system, compartment, or (sub) population of concern as a result of transport, partitioning, transformation, or degradation.
Guidance value	Value, such as concentration in air or water, that is derived after allocation of the reference dose among the different possible media (routes) of exposure. The aim of the guidance value is to provide quantitative information from risk assessment to the risk managers to enable them to make decisions. (See also *Reference dos*e)

Term	Description
Hazard	Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub) population is exposed to that agent.
Hazard assessment	A process designed to determine the possible adverse effects of an agent or situation to which an organism, system, or (sub) population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard, in contrast to risk assessment, where exposure assessment is a distinct additional step.
Hazard characterization	The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment and the second of four steps in risk assessment. Related terms: Dose–effect relationship, Effect assessment, Dose–response relationship, Concentration–effect relationship
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub) population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.
Margin of exposure	Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration. Related term: Margin of safety
Margin of safety	For some experts, margin of safety has the same meaning as margin of exposure, while for others margin of safety means the margin between the reference dose and the actual exposure. Related term: Margin of exposure
Measurement end-point	Measurable (ecological) characteristic that is related to the valued characteristic chosen as an assessment point.
Reference dose	An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime. Related term: Acceptable daily intake
Response	Change in the state or dynamics of an organism, system, or (sub) population in reaction to exposure to an agent.
Risk	The probability of an adverse effect in an organism, system, or (sub) population caused under specified circumstances by exposure to an agent.
Risk analysis	A process for controlling situations where an organism, system, or (sub) population could be exposed to a hazard. The risk analysis process consists of three components: risk assessment, risk management, and risk communication.
Risk assessment	A process intended to calculate or estimate the risk to a given target organism, system, or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterization (related term: *Dose–response assessment*), exposure assessment, and risk characterization. It is the first component in a risk analysis process.

Term	Description
Risk characterization	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub) population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.
Risk communication	Interactive exchange of information about (health or environmental) risks among risk assessors, managers, news media, interested groups, and the general public.
Risk estimation	Quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system, or (sub) population due to actual or predicted exposure.
Risk evaluation	Establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent, involving the complex process of determining the significance of the identified hazards and estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent. Risk evaluation is an element of risk management. Risk evaluation is synonymous with risk–benefit evaluation.
Risk management	Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard. Risk management comprises three elements: risk evaluation; emission and exposure control; and risk monitoring.
Risk monitoring	Process of following up the decisions and actions within risk management in order to ascertain that risk containment or reduction with respect to a particular hazard is assured. Risk monitoring is an element of risk management.
Safety	Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk.
Safety factor	Composite (reductive) factor by which an observed or estimated no-observed-adverse-effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: Assessment factor, Uncertainty factor
Threshold	Dose or exposure concentration of an agent below which a stated effect is not observed or expected to occur.
Tolerable daily intake	Analogous to *Acceptable daily intak*e. The term "tolerable" is used for agents that are not deliberately added, such as contaminants in food.
Tolerable intake	Estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub) population may be exposed over a specified period without appreciable risk.
Toxicity	Inherent property of an agent to cause an adverse biological effect.
Uncertainty	Imperfect knowledge concerning the present or future state of an organism, system, or (sub) population under consideration.
Uncertainty factor	Reductive factor by which an observed or estimated no-observed-adverse-effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: Assessment factor, Safety factor

Term	Description
Validation	Process by which the reliability and relevance of a particular approach, method, process, or assessment is established for a defined purpose. "Reliability" is defined as the reproducibility of outcome of the approach, method, process, or assessment over time. "Relevance" is defined as the meaningfulness and usefulness of the approach, method, process, or assessment for the defined purpose.

[1] This term is also contained in the list of IPCS key exposure assessment terminology—both definitions are consistent and interchangeable, depending on user preference.

8. ACRONYMS

AAQ	Ambient Air Quality
ADR	Australian Design Rules
ANZECC	Australian and New Zealand Environment and Conservation Council
BAM	Beta Attenuation Monitors
CAFE	Clean Air For Europe
CASAC	Clean Air Scientific Advisory Committee
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CSIRO	Commonwealth Scientific and Industrial Research Organisation
EAP	Environmental Action Program
EC	European Commission
EPHC	Environment Protection and Heritage Council
EU	European Union
FEV	Forced expiratory volume
GRUB	Generally Representative Upper Bound
HSI	Headline Sustainability Indicator
IGAE	Inter-governmental Agreement on the Environment
ISP	Issues Scoping Paper
JRN	Jurisdictional Reference Network
LOAEL	Lowest observed adverse effect level
NAAQS	National Ambient Air Quality Standards
NATA	National Association of Testing Authorities
NEPC	National Environment Protection Council
NEPM	National Environment Protection Measure
NGO	Non Government Organisations Advisory Group
NHMRC	National Health and Medical Research Council
NMMAPS	National Mortality and Morbidity air Pollution Study (USA)
NO_2	Nitrogen dioxide
NOx	Oxides of nitrogen
NOAEL	No observed adverse effect level
OAQPS	Office of Air Quality Planning and Standards
OECD	Organisation for Economic Co-operation and Development
O_3	Ozone
PAH	Polycyclic Aromatic Hydrocarbons
Pb	Lead
PRC	Peer Review Committee
PMS	Performance Monitoring Station
PM_{10}	Particles which have a mean aerodynamic diameter less than 10μm
$PM_{2.5}$	Particles which have a mean aerodynamic diameter less than 2.5μm

ppb	Parts per billion
ppm	Part per million
SEPP	State Environment Protection Policy
SO_2	Sulfur Dioxide
TSP	Total suspended particulates
TEOM	Tapered element Oscillating Microbalance
$\mu g/m^3$	Micrograms per cubic metre
US EPA	United States Environment Protection Agency
WHO	World Health Organization

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APPENDIX A: NEPC AND EPHC

National Environment Protection Council (NEPC)

The National Environment Protection Council (NEPC) is a national body established by State, Territory and Commonwealth Governments. The objective of the NEPC is to work cooperatively to ensure that all Australians enjoy the benefits of equivalent protection from air, water, soil and noise pollution and that business decisions are not distorted nor markets fragmented by variations in major environment protection measures between member Governments.

The NEPC stems from the Inter-Governmental Agreement on the Environment 1992, which agreed to establish a national body with responsibility for making National Environment Protection Measures (NEPMs). The NEPC and its operations are established by the National Environment Protection Council Act 1994 (Commonwealth) and corresponding State and Territory Acts.

NEPMs are broad framework-setting statutory instruments, which, through a process of inter-governmental and community/industry consultation, reflect agreed national objectives for protecting particular aspects of the environment. NEPMs may consist of any combination of goals, standards, protocols, and guidelines, although for the assessment of site contamination, the NEPC Acts specify that guidelines may be developed.

Implementation of NEPMs is the responsibility of each participating jurisdiction. A NEPM will take effect in each participating jurisdiction once it is notified in the Commonwealth of Australia Gazette, but is subject to disallowance by either House of the Commonwealth Parliament. Any supporting regulatory or legislative mechanisms that jurisdictions might choose to develop to assist in implementation of proposed NEPMs go through appropriate processes in those jurisdictions.

Environment Protection and Heritage Council (EPHC)

The Council of Australian Governments (COAG) agreed in June 2001 to the establishment of the Environment Protection and Heritage Council. The scope of activities of the EPHC incorporates the National Environment Protection Council (NEPC).

Since May 2002, NEPC has met in conjunction with the Environment Protection and Heritage Council. The functions of the statutory NEPC will continue under the EPHC as NEPC remains the legal entity for developing and making NEPMs.

APPENDIX B: CONVERSION BETWEEN µg/m³ AND PPM

Table A2.1 provides calculated conversion ratios for a number of specific criteria pollutants at 0°C and an absolute pressure of 101.325 kPa. These units were chosen to be consistent with clause 2 of the AAQ NEPM. These conversion ratios have been used throughout the document where necessary to allow comparison to current NEPM standards.

Table A2.1

Pollutant	ppm = µg/m³	µg/m³ = ppm
Carbon monoxide (CO)	1 ppm = 1250 µg/m³	1µg/m³ = 0.0008002 ppm
Nitrogen Dioxide (NO_2)	1 ppm = 2053 µg/m³	1 µg/m³ = 0.0004872 ppm
Ozone O_3	1 ppm = 2141 µg/m³	1 µg/m³ = 0.0004670 ppm
Sulfur dioxide (SO_2)	1 ppm = 2858 µg/m³	1µg/m³ = 0.0003499 ppm

The following equations were used when converting between µg/m³ and ppm.

$$C(ppm) = 0.022414\ x\ \frac{C(ug/m^3)}{MW(g)}\ x\left(\frac{T(K)}{273.15K}\ x\ \frac{101.325kPa}{P(kPa)}\right)$$

$$C(ug/m^3) = \frac{MW(g)\ x\ C(ppm)\ x\ 10^6}{22414}\ x\left(\frac{273.15K}{101.325kPa}\ x\ \frac{P(kPa)}{T(K)}\right)$$

These calculations rely on the basis that the molar volume of any ideal gas at standard temperature and pressure (0 °C and 101.325 kPa) is 22414m³/mol. Descriptions of the other variables include:

C(ppm) = concentration in parts per million

C(ug/m³) = concentration in micrograms per cubic meter

MW(g) = molecular weight in grams

P(kPa) = pressure in kilopascals

T(K) = temperature in Kelvin

APPENDIX C: THE NAAQS REVIEW PROCESS FLOW DIAGRAM