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Health Aspects of Air Pollution – answers to follow-up questions from CAFE

Report on a WHO working group meeting
Bonn, Germany, 15–16 January 2004

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ABSTRACT

Air pollution has a significant impact on human health in Europe. In order to design policies to decrease the health impacts of air pollution effectively, detailed knowledge on these effects is required. This WHO working group developed guidance for the European Commission to support the European Community Clean Air For Europe (CAFE) programme. It is supplementary to the report "Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide", which was published in spring 2003 by WHO.

The Working Group recognized that the large variations in individuals' susceptibilities within larger populations, when combined with more sophisticated (epidemiological) tools make it difficult to discern no-effect thresholds – which were previously widely used in establishing legally binding air quality standards – in population studies, and that the threshold concept may become meaningless at the general population level. Proper descriptions of concentration-response functions should be used instead. It also acknowledged the health relevance of both the exposure at hot spot locations, and the overall exposure of the population and recognized that an unequal distribution of health risks over the population would raise concerns of environmental justice and equity. The Working Group also recommended that the WHO Air Quality Guideline value for NO_2 of 40 µg/m^3 as annual mean should be retained or lowered. It also discussed different sources of uncertainties linked to the identification and quantification of health effects of air pollution in detail and concluded that the evidence is sufficient to recommend strongly further policy action to reduce levels of air pollutants including PM, nitrogen dioxide and ozone and that it is reasonable to assume that a reduction of air pollution will lead to considerable health benefits.

Keywords

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1. Introduction

Adverse impacts of air pollution on human health have been well documented. Effects may include several morbidity endpoints and a reduction of life expectancy by up to several months (WHO, 2002; WHO, 2003), with possibly some increased infant mortality in highly polluted areas. Concerns about these health effects and also effects on the environment have led to the implementation of various regulations to decrease the emissions of harmful air pollutants of their precursors on the international level (e.g. European Union Directives; protocols under the UNECE Convention on Long Range Transboundary Air Pollution), as well as the national, regional and local level. Additional measures – while necessary to further reduce the health effects by air pollution – are becoming increasingly expensive. As a consequence, there is an increasing need for accurate information on the impact of air pollution on health to underpin science-based, effective and well-targeted strategies to reduce these adverse impacts.

The World Health Organization (WHO) has in recent years investigated and reviewed the effects and impacts of environmental hazards on human health. The European Centre for Environment and Health of the WHO Regional Office for Europe has in particular investigated the health effects of ambient air pollution. Air Quality Guidelines (AQG) for Europe were published in 1987 and an update second edition in 2000 (WHO, 1987; 2000a). Different aspects of air pollution with particulate matter, ozone and nitrogen dioxide were reviewed recently (WHO, 2003). This review was supplemented by a meta-analysis of time-series studies of particulate matter and ozone (WHO, 2004). The aim of these guidelines and reviews is to provide a basis for the protection of public health from adverse effects of air pollutants and to eliminate or reduce exposure to those pollutants that are known or likely to be hazardous to human health or well being (WHO, 2000a).

2. Scope and purpose

The WHO project "Systematic Review of Health Aspects of Air Quality in Europe" aims to provide the Clean Air For Europe (CAFE) programme of the European Commission (DG Environment) with a systematic, periodic, scientifically independent review of the health aspects of air quality in Europe. As part of the project, WHO produced a report on "Health aspects of air pollution with particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2)" in early 2003 (WHO, 2003). In order to serve the needs of CAFE effectively, the findings of the review were presented in the form of short answers to concrete, policy relevant questions. In late spring 2003, WHO received a list of additional questions from the European Commission, which are relevant for the policy development within CAFE and which are complementary to the questions answered in the report mentioned above (WHO, 2003). The European Commission invited WHO to produce clear and succinct answers to these questions.

3. Process

In 2001, WHO agreed with the European Commission to provide the Clean Air For Europe (CAFE) programme (see also: http://europa.eu.int/comm/environment/air/cafe/index.htm) of DG Environment of the European Commission with a systematic, periodic, scientifically independent review of the health aspects of air quality in Europe. A Scientific Advisory Committee (SAC),

consisting of independent experts in the field of health effects from air pollution, was established by WHO to guide this review process. The members of the SAC are listed in Annex 1. To ensure transparency of the process, the minutes of each SAC meeting are either available on the internet at http://www.euro.who.int/eprise/main/WHO/Progs/AIQ/Activities/20020530_1 or may be obtained directly from WHO. The Committee supervised the review process and advised on its scope and methodology. It also assured a peer review of the scientific quality of the project's work. Until early 2004, two reports have been finalized:

- a report on "Health aspects of air pollution with particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2)" (WHO, 2003);

- a report on "Meta-analysis of time-series and panel studies of Particulate Matter (PM) and Ozone (O_3)" (WHO, 2004).

The CAFE Steering Group, which advises DG Environment of the European Commission on the strategic direction of the CAFE programme, has formulated specific additional questions to be addressed by the WHO process. These questions were forwarded to WHO in spring 2003. The questions are the following.

1. What is the health relevance and importance of <u>short-time exposure</u> to high peak levels or exposure in hot spots compared to <u>medium-term and long-term</u> exposure?

2. What are the uncertainties of the WHO answers, guidelines and risk assessment and how could these influence the conclusions for policy-makers?

3. Are there <u>specific population groups</u> (age categories such as children, adults, elderly, sensitive subjects, social groups) that should be brought into special attention?

4. What is the basis for maintaining the WHO NO_2 annual specific guideline value of $40ug/m^3$?

5. What other aspects of air pollution are important to address in the development of air pollution policy in Europe?

The CAFE Secretariat provided also some rationale to the questions, which was used to explore the different aspects and expectations embedded in the questions.

The SAC proposed the methodology and timetable of the process to derive answers to these questions, taking into account the guidelines provided in the WHO document "Evaluation and use of epidemiological evidence for environmental health risk assessment" (see: http://www.euro.who.int/air/Publications/20020621_9). The approaches chosen for answering the different questions differ slightly.

For questions 1 through 4, WHO invited designated experts to review the recent scientific evidence and to draft succinct answers supported by a justification (a rationale including references) using the most certain and most relevant scientific evidence. In the process of answering question 5, a small survey among experts was launched.

The drafts were discussed and revised at the fourth meeting of the SAC on 23 October 2003. At this meeting, the SAC recommended to investigate an additional question.

- What is the health relevance of the coarse fraction of PM ($PM_{10-2.5}$)?

This question was not formally received from the CAFE secretariat, but discussed at a CAFE stakeholder conference on particulate matter in autumn 2003; these discussions clearly indicated the importance of an answer to this question for the CAFE process.

All draft answers and rationales were subsequently sent out for a thorough peer review. The reviewers were both recommended by the SAC, which sought to recruit individuals who were knowledgeable about the relevant scientific fields, and nominated by members from the CAFE Steering Group. A list of reviewers can be found in Annex 1. The reviewers were instructed that they were acting in their capacity as experts and not as representatives of countries, agencies, universities, or other interest groups, and were provided with some guidance for the review. In particular, they were asked to assess the adequacy of coverage of the scientific evidence used in the papers and on the validity of the scientific evaluation. The guideline for reviewers can be found in Annex 2. All comments received from reviewers were collected by WHO and distributed to the members of the WHO working group well in advance of the meeting to allow an in depth analysis of the comments.

The WHO working group discussed the papers and the comments at the meeting held from 15 to 16 January 2004 in Bonn, Germany. The list of members of the working group can be found in Annex 1. Many comments resulted in small or sometimes significant changes in the final text. Even when a comment did not result in a change, the concerns, suggestions or criticisms expressed in the each comment were carefully evaluated.

During the meeting, the working group:

- agreed on the text of each of the answers

- provided guidance in regard to revisions of the rationale

- recommended specific follow-up activities to WHO.

A final draft of the report was once again sent out to all working group members for comments and approval.

4.   What is the health relevance and importance of <u>short-time exposure</u> to high peak levels or exposure in hot spots?

> **Explanation provided by the European Commission to this question:**
> WHO answers to the first set of CAFE question do to some extent address the issue. Presently WHO guidelines exist for both short term and long term exposure. The EC directives also have limit and target values for short term and long term averaging times, values that apply everywhere in ambient air. The follow-up question goes in two directions: 1) To what extent do hot spots contribute to the health burden to the general population and specific groups, such as those exposed close to hot spots? 2) What is the contribution to health burden of the high peak levels as compared to the more long-term (mean) exposure? The implications of the answers to the questions are far reaching for the setting of limit and targets values for air quality. (As an example, should the contributions of the hotspots and episodes on the health burden be small then the short-term and local measures as well as preventive temporary measures would receive lower priority in future strategies.)

Answer:

Adverse health effects have been documented after short-term exposure to peaks, as well as long-term exposure to relatively low concentrations of PM, ozone and NO_2. A direct comparison of the *health relevance* of short term and long-term exposures has been reported for PM, but not for ozone and NO_2. For PM, long-term exposure has probably a larger impact on public health than short-term exposure to peak concentrations.

Some studies have documented that subjects living close to busy roads experience more short-term and long-term effects of air pollution than subjects living further away. In urban areas, up to 10% of the population may be living at such "hot spots". The public health burden of such exposures is therefore significant. Unequal distribution of health risks over the population also raises concerns of environmental justice and equity.

Rationale:

Introductory remarks
Some definition is needed of "short-term peaks" and of "hot spots" before the question can be answered adequately.

We take "short-term" and "long-term" to indicate primarily the averaging times of the current short-term and long-term WHO Air Quality Guidelines and standards. Short-term is then one to eight hours for O_3; for NO_2, it is one hour; and for PM, it is 24 hours. "Long-term" is taken to indicate an averaging time of one year for each of these components. We accept that in it may be also be worthwhile considering different averaging times. However, as will be argued in more detail below, we do not think there is currently sufficient evidence to propose short-term Air Quality Guidelines that have different averaging times than the current WHO guidelines.

We interpret the question on "hot spots" to be about whether there are locations at which exposure to air pollution is significantly increased in comparison to urban background locations, short-term and/or long-term. So this part of the question refers to different spatial scales. We will focus the discussion of "hot spots" on roadside conditions. This is where much new evidence has been produced in recent years, and this is where important discussions with respect to regulation of NO_2 and PM are taking place. This does not imply that other "hot spots" near other local sources of pollution do not exist.

In keeping with the previous report, we will discuss this question for ozone, NO_2 and PM separately.

Ozone: Short-term versus long-term
There is ample experimental as well as epidemiological evidence that short-term (one to eight hours) exposure to peak levels of ozone is associated with transient reductions in lung function, with increased reporting of respiratory and eye symptoms, and with increased responsiveness to inhaled allergens. Recent contributions to our knowledge on this include a study among children with asthma (Gent et al., 2003) in which wheeze symptoms were found to increase significantly among maintenance medication users already at 1 hour ozone concentrations above 100 µg/m^3 and a California winter study in which asthmatic children were found to experience more symptoms with increased ozone that never exceeded 104 µg/m^3 as 1 hour maximum, and 74 µg/m^3 as 8 hour maximum (Delfino et al., 2003). Eye, throat and nose irritation were found to increase with 8 hour ozone concentrations never exceeding 121 µg/m^3 in asthmatic children studied in France (Just et al., 2002). Earlier work (e.g. Jorres et al., 1996) had already shown that

ozone increases allergen responsiveness in subjects with mild asthma or rhinitis. Such discomfort and morbidity effects are different from effects of long-term exposure to ozone which have primarily been associated with reduced lung function (Künzli et al., 1997; Peters et al., 1999), and they are also different from the effects of ozone seen in time series studies, which focus on increased hospital admissions for respiratory and cardiovascular disease and in some studies increased mortality (Thurston et al., 2001).

As documented in the previous report (WHO, 2003), time-series studies find linear or near-linear relationships between day-to-day variations in peak ozone levels and health endpoints, down to low levels of exposure. As there are usually many more days with mildly elevated concentrations than days with very high concentrations, the largest burden on public health may be expected with the many days with mildly elevated concentrations, and not with the few days with very high concentrations.

No analyses have been published to compare the relative public health significance of the short-term and long-term effects of ozone.

Ozone: Hot spots versus background
Being a secondary pollutant, ozone concentrations are usually not significantly higher at specific urban "hot spots". Higher concentrations can sometimes be detected in plumes downwind of strong emission sources of NO_x and/or NMVOC during summertime, when photochemical ozone production is enhanced. On the contrary, ozone levels tend to be lower in polluted urban atmospheres where ozone is depleted due to reaction with freshly emitted NO, often from traffic sources. Because this is due to the presence of pollutants some of which are harmful to health, this observation has no practical public health implications. For most practical purposes, there is no urban "hot spots" issue when it comes to ozone.

Nitrogen dioxide: Short-term versus long-term
For NO_2, there is experimental evidence that high concentrations increase bronchial responsiveness to inhaled allergens. A 30 minutes exposure to NO_2 concentrations of 500–750 $\mu g/m^3$ was shown to increase airway allergic inflammation and sensitivity to allergen exposure in subjects with mild asthma or allergic rhinitis (Tunnicliffe et al., 1994, Wang et al., 1995; Strand et al., 1997; 1998 Barck et al., 2002). A similar study conducted in the United Kingdom did not find such an effect when studying mild asthmatics at 400 $\mu g/m^3$ for six hours (Jenkins et al., 1999). Svartengren et al. (2000) showed that short-term exposure to air pollution in a road tunnel enhances the asthmatic response to allergen. Allergic asthmatic subjects were exposed during rest for 30 min in a busy city road tunnel. Subjects exposed to road tunnel NO_2 levels $\geq$ 300 $\mu g/m^3$ had a significantly larger early reaction following allergen exposure, as well as lower lung function and more asthma symptoms during the late phase compared to the reference exposure. Although a sizeable proportion of the population is sensitized to common allergens (6–24% for just four major allergens in the European Respiratory Health Survey (Jean et al., 2002)), the public health significance of such increases in responsiveness is uncertain, as patients with more severe disease have not been studied. Also, the experimental studies have been conducted at concentrations that are unlikely to be reached in ambient atmospheres. As discussed in more detail in the answer to Question 4, NO_2 in ambient air is part of a mixture of primary and secondary combustion products. Several studies have shown associations between NO_2 and mortality or morbidity endpoints in time series studies which are independent of the associations with PM or ozone (Peters et al., 2000; Burnett et al., 1998; 1999). Associations with long-term exposure to mixtures represented by NO_2 have been reported with respiratory morbidity as well

as cardio-respiratory mortality endpoints (e.g. Hoek et al., 2002; Schindler et al., 1998; Brauer et al., 2002; McConnell et al., 2003). Effects of both long-term and short-term exposures to ambient mixtures of combustion products represented by NO_2 are of concern. As with ozone, no analyses have been reported on the relative public health significance of short-term and long-term exposures to NO_2.

Nitrogen dioxide: Hot spots versus background
"Hot spots" for nitrogen dioxide will be dealt with PM in a joint paragraph (see below).

Particulate matter: Short-term versus long-term
Effects of long-term exposure to PM on mortality are of prime concern, as discussed previously (WHO, 2003). It has been estimated that long-term exposure to moderate levels of fine PM can be associated with a reduction in life expectancy of up to several months.

Effects of short-term exposure to PM have been documented in numerous time series studies on mortality and morbidity endpoints. Again, the evidence has been discussed before (WHO, 2003).

Consequently, both short-term and long-term effects of exposure to PM are of concern. In contrast to ozone and NO_2, there have been analyses published on the relative public health significance of short-term and long-term exposures to PM. "Disability Adjusted Life Years" (DALYs) have been estimated for both types of effect, and the analysis suggests that the public health significance of the long-term effects clearly outweighs the public health significance of the short term effects (de Hollander et al., 1999). This obviously does not diminish the significance of the short-term effects of PM, which consist of very large numbers of attributable deaths and cardiovascular and respiratory hospital admissions in Europe.

Particulate matter and nitrogen dioxide: Hot spots versus background
This question of "hot spots" relates to the relevance of spatial differences in exposures, i.e. the importance of location and proximity to emission sources. This issue is of relevance for NO_2 and PM (also for other pollutants such as CO which are not being further discussed here). NO_2 can be significantly elevated near sources of NO_x, especially near busy roads. The same is true for PM, and then especially PM components such as elemental carbon and ultrafine particles which are considerably elevated near traffic sources. Recent evidence has shown that subjects living near busy roads (the best investigated type of hot spot) are insufficiently characterized by air pollution measurements obtained from urban background locations, and that they are also at increased risk of adverse health effects (Roemer and van Wijnen 2001; Venn et al., 2001; Hoek et al., 2002; Garshick et al., 2003; Janssen et al., 2003; Nicolai et al., 2003). It is worth noting that a significant part of the urban population may be affected. Roemer and van Wijnen (2001) estimated that 10 % of the population of Amsterdam was living along roads with more than 10 000 vehicles a day. Increased risks at hot spots raises concerns about an unequal distribution of risks connected to involuntary environmental exposures. This may affect in particular socially disadvantaged groups; a California study has shown that socially disadvantaged children have a higher chance of living close to major roads (Gunier et al., 2003).

In addition, the vast majority of epidemiological studies characterize exposure with measurements that describe urban background concentrations rather than concentrations at locations influenced by sources in the immediate vicinity. Thus, the effect estimates may not sufficiently include effects due to local hot spots. Even when measurements would be conducted near hot spots, especially busy roads, there are good indications that these hot spots are

insufficiently characterized by measurement of the currently regulated PM_{10} metrics, not even by the contemplated $PM_{2.5}$ metric. For that reason, WHO recommended already in response to the previous set of CAFE questions to give further consideration to black carbon or other measures of traffic "soot" (WHO, 2003). Also, further investigations are needed on effects of ultrafine particles (particles with a diameter smaller than 100 nm). Ultrafine particles have been shown to be greatly elevated near busy roads (e.g. Hitchins et al., 2000). Some studies have suggested adverse health effects of ultrafine particles at ambient concentrations (e.g. Peters et al., 1997); consequently, there is a need to address exposure to ultrafine particles as one of the possible PM characteristics important for the adverse effects observed at roadside "hot spots".

5. What are the uncertainties of the WHO answers, guidelines and risk assessment and how could these influence the conclusions for policy-makers?

5.1 Introductory remarks

Currently, no answer can be given to Question 2 in absolute terms that would cover all different aspects of the problem. Uncertainties linked to gaps in knowledge exist and will exist in the future. We are aware of the uncertainties and we tried to take them into account to our best knowledge when deriving our conclusions on the questions we received from CAFE. To address the uncertainties in a systematic way, the project followed the advice provided by the WHO guideline document "Evaluation and use of epidemiological evidence for environmental health risk assessment" (WHO, 2000b), and in particular its recommendations in section 4.2. In particular, the process of the present project:

- developed and followed the protocol for the review;

- identified and assessed validity of the relevant studies;

- conducted systematic overview of evidence from multiple studies, including formal meta-analysis;

- based its conclusions on the critical scientific judgment of a wide range of top scientists working in various disciplines related to the assessment of impacts of air pollution on health.

The working group felt that an attempt to quantify the uncertainties linked to all answers to the first round of CAFE questions was – if at all – not feasible within this project. However, the European Commission provided some additional information relating to issues where an in depth assessment of underlying uncertainties was felt necessary.

Proper treatment of uncertainties is an important part of all risk management. Current uncertainties related to the scientific evidence should however not be taken as a cause for not acting if the potential risks are high and measures to reduce the risks are at reasonable cost (precautionary principle). As part of the WHO review the main uncertainties should be identified and assessed either in quantitative or qualitative terms. A number of issues are related to the uncertainties such as the following.

– It appears possible that studies that have found no associations between particulate matter concentrations and mortality or morbidity have not been published. How has the expert group tackled the issue of a potential publication bias?

– In some areas there appears to be evidence pointing in different directions thus an indication of the certainty of the conclusions would be desirable. An example would be the issue of threshold for effect due to exposure to ozone where some epi-studies have not been able to identify a threshold whereas thresholds have been found in toxicological studies. The uncertainty on the existence or non-existence of a threshold for ozone may influence the guidelines and also the setting of EC air quality standards. Hence, it is important to have an understanding how the strength of evidence and the uncertainty influences the guidelines.

– The WHO first report put a clear emphasis on the health effects of small PM originating from combustion sources. Can these relationships be quantified giving the source contribution to health effects? How may uncertainties in the source apportionment and the particle characterization (size and composition) influence the quantitative assessment of pinpointing a source as being the contributor to health effects? Also, is there information and associated uncertainty on the health effects of specific secondary particle mass, such as the particle mass fraction due to agriculture activities leading to ammonia containing particles.

– In the review of the guidelines a systematic assessment of the uncertainties (such as confidence intervals) of the relative risks would give a better understanding of the degree of uncertainty. This item should also include the uncertainty in the application of different models (including GAM).

– The assessment of the risks builds on a concentration response relationship based on a number of studies from the United States and Europe. However, different parts of Europe have different mixes of air pollution due to differences in sources, climate and so forth. To what extent may uncertainties of the applicability of these relations influence the risk assessment due to particles and other priority pollutants?

The working group focused its discussions on uncertainties on the subjects highlighted in this statement. These individual aspects of uncertainties are discussed in the following parts of the answer to this question on uncertainty.

5.2 Consideration of publication bias in the review

Explanation provided by the European Commission to this question:
It appears possible that studies that have found no associations between particulate matter concentrations and mortality or morbidity have not been published. How has the expert group tackled the issue of a potential publication bias?

Answer:

Publication bias occurs when the publication process is influenced by the size of the effect or direction of results. The bias is usually towards statistical significant and larger effects. It can be detected and adjusted for using statistical techniques. Bias may also occur when literature is selectively ascertained and cited.

This review used a systematic approach to identify all short-term exposure studies, but it did not formally investigate publication bias. The reviewers were aware that evidence of publication bias has been identified in meta-analyses of single city time series studies, but when estimates were corrected for this bias, significant positive associations remained. Furthermore, the multi-city time series studies, which have published results from all participating cities and are free from publication bias, have reported significant positive associations.

Because of the size and experience of the review group and referees, it is unlikely that any important published long-term study has been missed. Formal assessment of a possible publication bias has not been undertaken. Every effort was made to systematically ascertain long-term exposure studies.

Rationale:

At a meta-analytic level, i.e. when the collectivity of studies is considered, various sources of bias are possible. For example, the studies reviewed may be unrepresentative of the totality of those that have been carried out. This might occur because: 1) not all published studies have been ascertained for review; 2) because published studies are not representative of all work done because some studies remain unpublished; or 3) because the reviewer draws biased conclusions from the published work.

In the WHO review, several methods were used to reduce bias. The time-series studies reviewed were obtained by systematic methods of literature searching and we ensured that all relevant published studies in any language were obtained, following the WHO guideline document on the evaluation and use of epidemiological evidence for environmental health risk assessment (WHO Working Group, 2000). Studies with grossly inadequate methods were excluded. "Grey" literature (unpublished reports) was not obtained and authors of published work were not asked for additional results.

One is left however with the question posed by CAFE, which is whether there is an indication that published evidence is different from the totality of research findings. This is a common if not universal problem in our research culture (Sterling 1959; Mahoney, 1977; Simes & Berlin, 1988; Begg & Berlin, 1988; Begg & Berlin, 1989; Dickersin, 1997). It arises because there are more rewards for publishing positive or at least statistically significant findings, and journals are likewise biased towards "interesting" rather than "negative" findings. In parenthesis, this is interesting in view of the prevalent Popperian view of the scientific process as one of falsification rather than confirmation.

In the case of population studies there are particular reasons why publication bias might occur. One is that the data are relatively cheap to obtain and analyse, so that there may be less determination to publish "uninteresting" findings. The other is that each study can generate a large number of results for various outcomes, pollutants and lags and there is quite possibly bias in the process of choosing among them for inclusion in a paper.

In the field of air pollution epidemiology, the question of publication bias has now begun to be formally addressed (Anderson et al., 2002; Peacock et al., 2002). An additional paper addressing this issue is currently under consideration by an epidemiological journal. This cannot be made available at the present time.

Recognizing the potential for bias was one aspect of the rationale for the Air Pollution and Health: a European Approach 2 (APHEA 2) study, which had a prior commitment to publish and an a priori approach to choice of lag and analytic strategy. Analyses for all cities were done by one centre for one group of outcome, blind to the identity of the cities being analysed. Thus, this prospective multicity study attempted to avoid analytic bias, lag selection bias and publication bias.

There are methods of detecting publication bias but it should be noted that these are not without problems. One method is the "funnel plot" in which estimates are plotted against their standard error or precision of the estimate. If there is no publication bias, the resulting scatter should be symmetrically shaped like a funnel (Light & Pillemer, 1984). Evidence of asymmetry in the funnel plot can be tested by several statistical techniques (Egger et al., 1997; Begg & Mazumdar, 1994). There may be other reasons apart from publication bias for an asymmetrical funnel plot, so while the presence of symmetry probably excludes any important degree of publication bias, the presence of asymmetry, while suggestive of publication bias does not prove it.

An example of a funnel plot showing asymmetry is shown in Figure 1 for black smoke and daily all-cause mortality. There is clear asymmetry in the funnel plot. The formal test of bias is highly statistically significant. In contrast when a similar plot (Figure 2) is done for the 17 PM_{10} and daily mortality studies reviewed in the WHO Air Quality Guidelines for Europe (WHO, 2000), there was no asymmetry and the test for asymmetry was non significant ($p<0.51$).

As a final example, a funnel plot and test for publication bias for $PM_{2.5}$ and daily mortality in North American studies (Figure 3) is presented. This shows some evidence of some publication bias in the studies with lower power. It is not very strong and the formal test was not significant. The summary estimate was not affected, being heavily weighted by the large studies towards the left of the axis.

It is important to distinguish two different implications of publication bias. The first is for science and hazard detection. Publication bias could lead to a false conclusion being drawn as to the association between air pollution and a health outcome i.e. that there is an association when in fact there is none. In the case of black smoke and daily mortality, correction for bias using the trim and fill method reduced the estimate of effect from 0.6% to 0.5% increase in mortality for a 10 unit increase in pollution. The trim and fill technique replaces the "missing" studies and re-calculates the estimate (Duval & Tweedie, 2000). However the adjusted estimate remained significant (0.5%; 95% CI: 0.3–0.6), suggesting that an association remains after allowing for publication bias in this way. More important are the results of the multicity studies (National Morbidity, Mortality, and Air Pollution Study, NMMAPS from the United States of America and APHEA) which are free from evidence of bias and provide significant, though somewhat lower results than those from single city studies.

The other implication of publication bias is inflation of the real effect. This would clearly have implications for health impact assessment, but does not in itself affect the conclusions in the

WHO review. For health impact assessment it would be necessary to recognize the possibility of publication bias and adjust for it where possible.

Bias due to preferential selection of models with positive result
Another related issue that may result in distortion of exposure-response coefficients and be revealed in funnel plots is preferential lag selection for positive effects. Often, air pollution time series studies investigate several "lags", i.e. delays between exposure and effect. If investigators report the most significant and/or largest effect estimate in a positive direction, effect estimates as published in the literature may be inflated. If the most significant effects in either direction are reported, bias does not occur. In principle, this is not an issue in planned multicentre studies which use predefined lags. The NMMAPS and APHEA studies found significant exposure-response relationships using such a planned approach (Samet et al., 2000; Katsouyanni et al., 2001). The problem with the latter approach is that the best fitting models may not be chosen. This issue can be resolved by using all of the lags to estimate the effects associated with a distributed lag.

Bias due to use of single day rather than cumulative lags
On the other hand it is important to recognize that the use of single day lags may result in underestimation of exposure-response relationship because air pollution may exert an effect over longer periods of time. An analysis addressing the effect of using different lag structures suggested that indeed, multi-day exposures were associated with larger effect estimates than single-day exposures (Zanobetti et al., 2000; Schwartz, 2000). As shown by these authors, using single day lags can easily result in underestimation of effect estimates by a factor of two. However, it was also shown that the lag-structure might be different for different health endpoints and might vary between being immediate or cumulative over several lags. Therefore, pre-selected mis-specified lags might result in valid tests, but may underestimate the effects. Also, the recent work on "harvesting" (as discussed more fully in our answers to the previous set of CAFE questions) has suggested that estimates of air pollution effects in time series studies may increase even further when taking into account longer averaging times for exposure.

Bias due to measurement error
Measurement error in exposure often leads to underestimation of effects of exposure on health. A recent analysis has suggested that sizeable underestimation of exposure-response coefficients may occur in time series studies of air pollution and mortality for this reason (Zeger et al., 2000). However bias away from the null is possible when statistical models contain multiple possibly correlated pollutants (Zeger et al., 2000).

Fig. 1: Funnel plot of black smoke and daily all cause mortality in 47 studies. This shows an asymmetrical distribution suggestive of publication bias. A formal test of bias was significant p<0.001. Correction for bias using the method of Duval et al (2000) reduced the summary estimate from 0.6% to 0.5% increase in deaths per 10μg/m^3 black smoke.
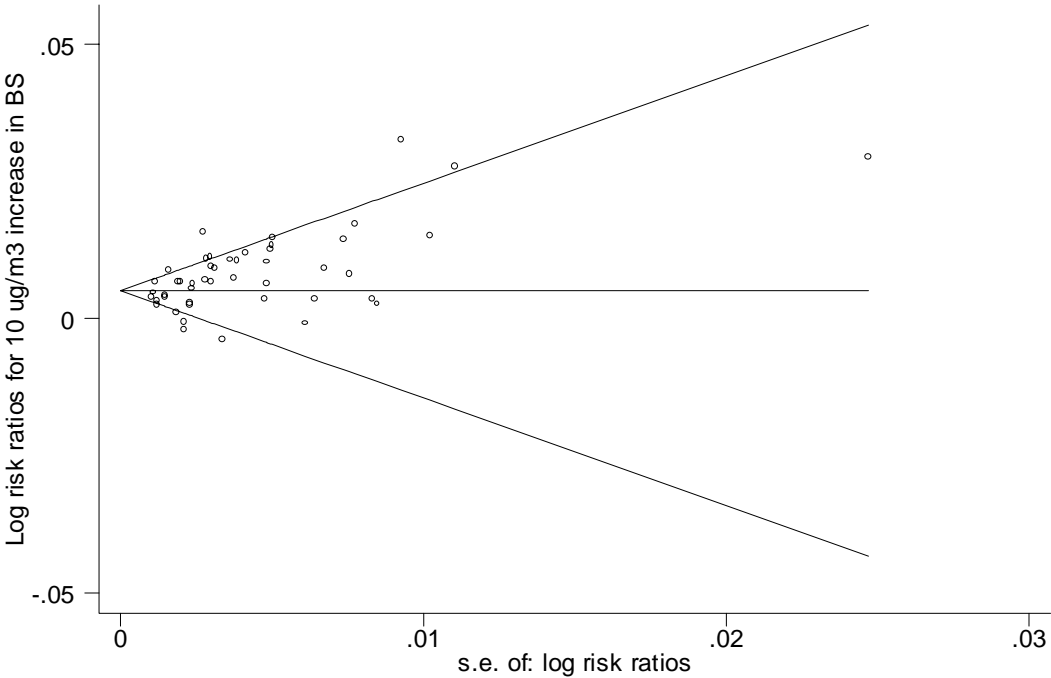
Fig. 2: Funnel plot of studies of PM$_{10}$ and daily mortality used in the WHO (2000). There is no evidence of bias in the test or the formal plot.
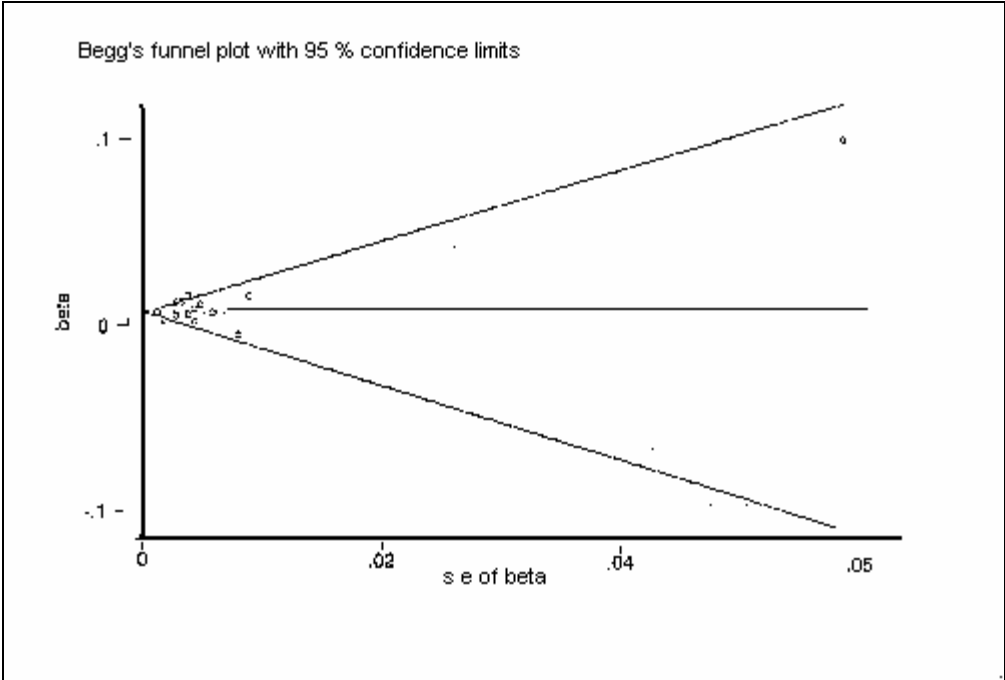
Fig. 3: Funnel plot of PM$_{2.5}$ and daily mortality in North American studies. There is moderate evidence of some bias. Formal test not significant (p<0.08).

Begg's funnel plot with pseudo 95 % confidence limits
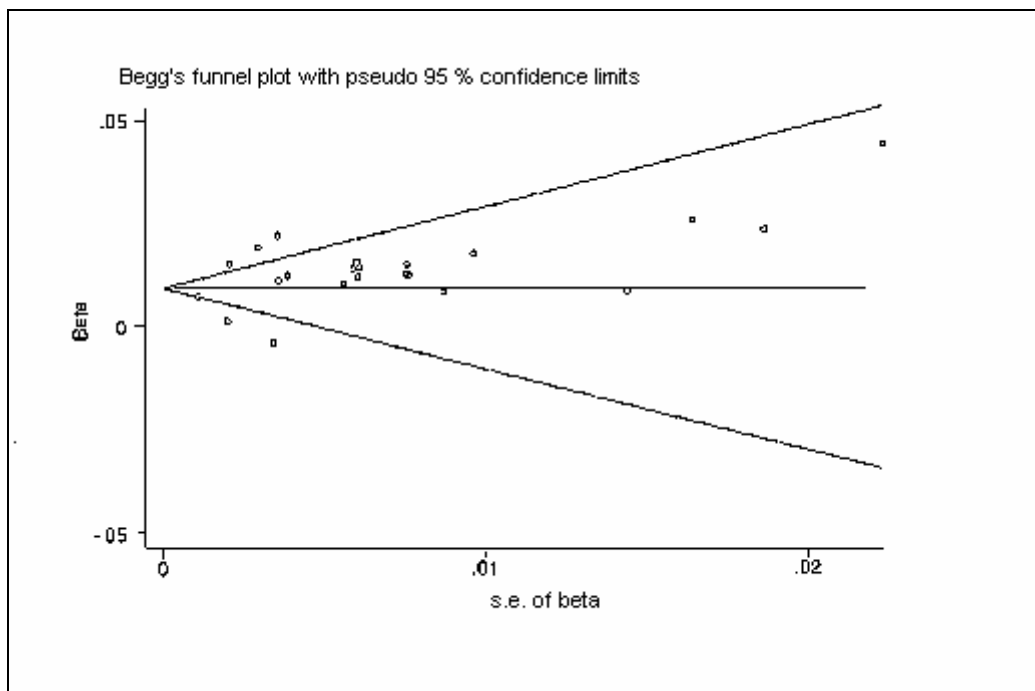
5.3 Consistency of epidemiological and toxicological evidence in defining thresholds

Explanation provided by the European Commission to this question:
In some areas there appears to be evidence pointing in different directions thus an indication of the certainty of the conclusions would be desirable. An example would be the issue of threshold for effect due to exposure to ozone where some epi-studies have not been able to identify a threshold whereas thresholds have been found in toxicological studies. The issue of thresholds could be reassessed for different health endpoints.

General statement:

Multiple factors determine whether a threshold is seen and the level at which it can occur. Exposure-response curves depend on the age and gender of the subjects, their health status, their level of exercise (ventilation) and, especially the health effect selected. For highly uniform population groups, with a specific exposure pattern, a full range of concentrations, and a specific health outcome, one could identify a specific threshold. However, when there are different exposure-response curves for different groups, thresholds are harder to discern in population studies, and may ultimately disappear. Therefore, the evidence coming from the epidemiological and toxicological studies is not contradictory.

Rationale:

This section contains a description of the determinants of thresholds and tends to demonstrate why they are sometimes evident and at other times are difficult or impossible to detect. As summarized in the second sentence of the general statement, it is true that thresholds have sometimes been delineated in clinical studies of healthy human subjects to ozone when changes

in pulmonary function or bronchoalveolar lavage constituents have been selected as endpoints. It is also true that, in contrast, in epidemiologic studies where death or hospital admissions have been used in non-uniform populations, no threshold levels were identified. However, this is likely to be a consequence of different experimental designs and does not reflect inherent contradictions between the studies.

In brief, when the multiple factors controlling the health outcome measure are controlled and uniformity is achieved, thresholds will be evident. For example, human or animal dose-response curves are most likely to exhibit a threshold when:

1. the subjects are genetically similar

2. the exposure is controlled

3. the exposure is to a single pollutant

4. the subjects are healthy, have no infection or pre-existing disease

5. the subjects have similar ventilation rates

6. the subjects have the same diet

7. there are minimal lifestyle differences (smoking, obesity)

8. gender and age are controlled.

Mathematical analyses have shown that if one sums many individual exposure response curves, all of which may have thresholds, then the threshold will gradually disappear and a more linear response will take its place. In other words, (1) as the characteristics of the animal or human subjects being studied become more varied and (2) as the exposure patterns become more varied and complex and (3) as we add various susceptible groups (children or the elderly or individuals with pre-existing cardiopulmonary disease), thresholds may be harder to discern and may ultimately disappear.

It should also be pointed out that the location of a threshold described in terms of levels depends on the health outcome selected. Higher exposure levels might be needed to produce mortality. Lower levels will be needed to achieve significant changes in respiratory symptoms, respiratory function, or hospital admissions and still lower concentrations will need to find the threshold for modest inflammatory changes (increased protein content or increased numbers of neutrophils in bronchoalveolar lavage (BAL)).

We would not assert that there is no possible threshold for any pollutant related health effect. What epidemiologic studies show, however, is that when complex populations of humans are studied, it is often not possible to identify a threshold at the range of concentrations currently being studied. Thus, in many published studies, authors feel confident in asserting that no threshold was apparent at current levels. This is not to say that no threshold exists at any level.

Toxicology and epidemiology rely on the concept that there is a dose/response relationship. This relationship can be described in uniform or more varied groups of animals and humans and with well-characterized or poorly characterized exposures. However, it is important to realize that there are susceptible individuals who show different dose-response slopes (see also answer to the question on specific population groups in this report). For example, if a condition exists in the population in the absence of environmental exposure, such as cardiovascular disease, and the pollutant of interest exacerbates or contributes to the mechanisms of disease that yield an

outcome, such as sudden cardiac failure, then the concept of threshold is meaningless at the population level. In contrast, thresholds are often observed in animal studies because of the tight regulation of the exposure and of the exposed population (inbred mouse strains). However, when toxicology studies include "susceptible" animals we observe different dose/response slopes.

Studies of mechanisms of toxicity also reveal plausible underlying processes that could alter the dose/response relationship. These include adaptation of parts of the pulmonary response to ongoing oxidative stress-producing pollutants that could transiently alter the dose response curve.

Epidemiologists have grappled with the issue of thresholds. For example, the relationship between daily deaths and airborne particles in 10 United States cities has been analysed (Schwartz, 2000). Schwartz points out that there is variability in particle composition (e.g. summer/winter differences) as well as variability in the causes of death. The most frequent causes include myocardial infarctions, arrhythmias, and pneumonia. Each outcome may have a unique dose–response. Moreover, exposed humans vary widely in their susceptibility. Thus, the totality of this heterogeneity makes certain that a threshold will be difficult or impossible to define at the particle concentrations experienced.

The existence of a "threshold" implies a concentration-risk relationship with no effect until a "threshold" concentration is crossed; then risk rises. In analyzing epidemiological data to determine the existence of a threshold, comparison should be made between a statistical model incorporating a threshold and one not incorporating a threshold. Model fit can then be assessed, both descriptively and more formally. Alternatively, methods can be used to search for "break points" or inflections in the concentration-risk relationship. The data can also be restricted to lower and lower levels with repeated analyses to determine if an effect persists. Few epidemiological studies have been analysed using these approaches.

Most epidemiological data sets are analysed with linear models, which inherently assume no threshold. In interpreting the findings of such models, an estimate that is not statistically significant is not evidence for a threshold, even though this interpretation may be offered. Rather, the risk estimate from a linear model is indicative of a threshold if the estimate is close to the null and precisely estimated, i.e. the confidence intervals are narrow. While epidemiological data have been the primary basis for empirical determinations of dose-response relationships in humans, studies on mechanisms is the foundation for interpreting the epidemiological evidence.

The reasoning throughout this discussion is consistent with what most toxicology books say about thresholds. Rodricks et al. (2001) point out that for most non-cancer endpoints, there probably is a small dose of chemical that can be tolerated without any adverse health effects. In other words, there should be a threshold. However they go on to say, "Threshold doses generally cannot be estimated with precision even in animal studies with homogenous animals. Estimation of threshold doses for a heterogeneous human population is even more problematic".

In conclusion, we recognize that thresholds are an appealing concept. It would be reassuring if we could define a concentration level below which there are no adverse health effects. However, contemporary data in the area of air pollution suggests that this concept is elusive. Realistic heterogeneity causes thresholds to vanish. Thus, we believe that regulators need to accept the reality that laboratory scientists and epidemiologists can help provide dose-response and concentration-response curves which will reveal the extent to which reductions in pollution

levels will result in reductions in a specific health outcome. It is also the case that this concentration-response function will be best determined at concentrations that occur. Extrapolating to lower concentrations or doses where data do not exist will however increase the uncertainty.

Ozone:

Chamber studies may show thresholds for mean effects of ozone on lung function and airway inflammation but a few individuals show these responses below these levels. As mentioned previously, a particular threshold in a particular experimental situation does not necessarily contradict a finding of effects below these levels in other situations.

The time-series results often have insufficient data to distinguish between a linear and non-linear model with confidence. In addition, the statistical analyses applied to investigate thresholds in datasets on particles have not been applied to the same extent to datasets on ozone. There remain uncertainties in interpreting the shape of exposure-response relationships in epidemiological studies due to different patterns of confounding by other pollutants and correlations with personal exposure across the range of ozone concentrations. Although there is evidence that associations exist below the current guideline value, our confidence in the existence of associations with health outcomes decreases as concentrations decrease.

The answer and rationale refer to acute effects of ozone, as this is most important for health impact assessment of the effects of ozone.

Rationale:

Clinical experimental studies
Experimental clinical studies have the advantage that it is possible to set experimental conditions to test a specific hypothesis. Particular subject groups can be selected (provided ethical considerations are met), ozone can be studied without the presence of other pollutants and ozone concentrations can be experimentally controlled. These studies may give clearer information about a threshold for a specific measure of effect in particular circumstances. Such results can be used to test conclusions from other studies such as ecologic air pollution studies. However, the applicability of this information to the whole of the general population is limited as the studies usually have a small sample size and only study healthy or mildly ill subjects and milder health outcomes.

Human clinical studies do not provide convincing evidence for an absolute level below which no effects are observed. There is evidence that prolonged (6.6 hours) single exposures to ozone at concentrations of 160 µg/m^3 (80 ppb), with prolonged "moderate" exercise, cause decrements in pulmonary function, airway injury, and increased non-specific airways responsiveness. Although the magnitude of the mean effects at this exposure level is generally small, some individuals show clinically important responses.

McDonnell et al. (1995) developed a predictive model for changes in the forced expiratory volume in 1 second (FEV$_1$) based on the 6.6-hour ozone exposure studies performed by the US Environmental Protection Agency. This model found that the lowest level of exposure, expressed as concentration x time for which the 90% confidence interval excluded 0, was 0.4 mg/m^3-hour (0.2 ppm-hour). This model suggests that significant declines in FEV$_1$ would be seen with exercising exposures to ozone concentrations of 400 µg/m^3 (200 ppb) for one hour, or 50 µg/m^3 (25 ppb) for eight hours. This result is consistent with the epidemiological and panel studies

finding effects on lung function with ozone concentrations below the WHO Air Quality Guidelines of 120 µg/m^3 (60 ppb) for eight hours.

It must be kept in mind that human subjects show highly variable responsiveness to ozone effects (see also answer to Question 3). This may be the result of genetic differences as described in the epidemiological studies section below. Clinical studies have generally used relatively small numbers of unselected subjects. Relying on mean changes for the whole subject group may underestimate the clinical significance of larger changes in a small number of subjects. If a clinical study were to be performed with pre-selected "responders" to ozone, in terms of pulmonary function, it is likely that the observed response thresholds for such groups are lower than that for a healthy, unselected group. Thus the human clinical data on lung function changes are not sufficient to indicate a threshold below which no effects are expected to occur for all people.

With regard to indices of airway inflammation and injury, fewer data are available than for the studies of lung function effects. However, the report by Devlin et al. (1991) shows that 6.6 hours of exposure, with exercise, to 160 µg/m^3 (80 ppb) ozone caused statistically significant increases in inflammatory cells in bronchoalveolar lavage fluid, and increases in indicators of epithelial injury. The degree of change was less than that generally seen with higher concentrations, and some significant changes at higher concentrations were not seen with exposure to 160 µg/m^3. However, two study subjects exposed to 160 µg/m^3 ozone experienced greater than 10-fold increases in polymorphonuclear leukocytes in bronchoalveolar lavage (BAL) fluid, suggesting an increased sensitivity to ozone inflammatory effects in these subjects. It is possible that the effect threshold for inflammatory changes in such sensitive subjects may be well below 160 µg/m^3.

Epidemiological studies
Observational epidemiological studies examine whole populations including susceptible groups (even if these are unidentified). However, as the population is being observed in real life, it is not possible to choose perfect experimental conditions. The ideal case where only the ozone concentration is changed is not possible because, in actuality, changes in ozone concentrations occur at the same time as changes in the weather and concentrations of other pollutants. In addition, the study has to work with whatever range of ozone concentrations happen to occur in a particular place.

Time-series results often have insufficient data to distinguish between a linear and non-linear model with confidence. This can result from factors including too few data points overall, too few data points near a possible threshold and a restricted range of data. It is possible to perform a statistical test for any significant deviation from linearity but this has only been performed in a minority of studies on ozone (e.g. Schwartz et al., 1994; Hoek et al., 1997). In addition, the sophisticated statistical analyses applied to specifically address the question of thresholds in datasets on particles (e.g., Daniels et al., 2000) have not been applied to datasets on ozone to the same extent. A recent paper (Kim et al., 2004) applied a linear model, a natural spline model and a threshold model to a dataset in Seoul and found that the threshold model, with a threshold at 56 µg/m^3 (28 ppb) 1 hour average, gave the best fit. However, the slope above the threshold was steeper than in the linear model so the threshold model did not necessarily predict a lower health impact. Further studies of this type are needed. Currently, many studies on ozone do not explicitly describe the shape of the exposure-response function at all.

The atmospheric chemistry of ozone has some unique features which make the interpretation of the shape of exposure-response relationships particularly complex. Formation of ozone is temperature-dependent so that the high end of the exposure-response relationship will be based on hot sunny summer days and the lower end on winter days. Unfortunately, this may mean that factors other than the ozone concentration are varying across the range of the exposure-response relationship. For example, it is known that ozone is often positively correlated with particles in the summer and negatively correlated with particles in the winter (Sarnat et al., 2001). Ozone can be particularly low in cold inversion conditions when other pollutants accumulate. As these other pollutants can have the same health effects as ozone, this can give the perverse impression that health effects <u>increase</u> (or fail to drop) as ozone concentrations decrease. This may appear to suggest a change in slope in a single pollutant model exposure-response relationship that does not truly reflect the effect of ozone itself. Although the use of multi-pollutant models may help to disentangle this somewhat, there may be other factors involved as well. For example, variations in the total oxidant burden in the different polluted environments in which ozone occurs may influence the health response to ozone.

Ozone levels are very low indoors. This means that people's exposure to ozone varies according to how much they are outdoors. It is likely that people spend less time outdoors on the winter days contributing to the lower end of the exposure-response relationship – another factor complicating interpretation. The low level of ozone indoors means that personal exposure to ozone and ambient concentrations of ozone are not well correlated (Sarnat et al., 2001; Avol et al., 1998). Brauer et al. (2002) demonstrated, using simulations, that surrogate metrics that are not highly correlated with personal exposures obscure the presence of thresholds in epidemiological studies of larger populations. This would apply when ambient ozone concentrations are used as a surrogate for personal exposure to ozone.

Bearing in mind the above difficulties in interpretation, individual studies that examined the shape of exposure-response relationships are described below. Emphasis is given to studies on all cause mortality, respiratory hospital admissions and respiratory symptoms, the endpoints most likely to be used in health impact assessment. Panel studies that examine effects on lung function at a similar range of ozone concentrations are also considered as these may lend plausibility to the occurrence of the other health outcomes in the same range.

Several studies of ozone and all-cause mortality in single pollutant models suggest thresholds at 40 to 100 $\mu g/m^3$ (20–50 ppb) 8 hour average (Anderson et al., 1996; Hong et al., 1999; Wong et al 2001); 50 $\mu g/m^3$ to less than 120 $\mu g/m^3$ 1 hour average (Kim et al., 2004; Simpson et al., 1997; Morgan et al., 1998/2002) or 36 to 50 $\mu g/m^3$ 24 hour average (Diaz et al., 1999; Goldberg et al., 2001). Morgan et al. (2002) found a linear association when using the GAM rather than GEE model. Galan Labacca et al. (1999) found a U-shaped relationship and Toulomi et al. (1997) found a flatter slope at high concentrations. However, for the reasons given in the paragraphs above, it may not be possible to take these shapes at face value.

Fairley et al. (2003) found a suggestion of a stronger relationship of all cause mortality with daily ozone ppb-hours above 120 $\mu g/m^3$ after adjustment for $PM_{2.5}$. Kim et al. (2004) found that there was a steeper slope above 52 to 56 $\mu g/m^3$ 1 hour average in several different multi-pollutant models. Although Moolgavkar et al. (1995) only found a significant association, adjusted for SO_2 and TSP, in the highest quintile (above 96 $\mu g/m^3$ 24 hour average), there was a linear increase across quintiles. Borja-Aburto et al. (1997) found no relationship after adjustment for TSP. Only Hoek et al. (1997) used a multi-pollutant model (with TSP/24 hour average ozone)

and a formal test for non-linearity – the test for non-linearity was not significant. The relative risk remained similar even after all days above 40 µg/m^3 ppb 24 hour average were removed.

For single pollutant models of respiratory hospital admissions, Ponce de Leon et al. (1996) found a suggestion of a threshold around 100 µg/m^3 8 hour average; Thurston et al. (1994) found increased relative risks in the two upper quartiles above 90 µg/m^3 1 hour average and Schwartz et al. (1994) found an increase in risk above 50 µg/m^3 24 hour average. Other studies found a flat association (Atkinson et al., 1999, 8 hour) or a linear association (Burnett et al., 1994; Burnett et al., 2001, 1 hour). Burnett et al. (1997) found an upturn at 50 µg/m^3 12-hour average but a chi-squared test for non-linearity was not significant. None of the studies examined the shape of the exposure-response in a multi-pollutant model.

Mortimer et al. (2002) found that a significant association with lower respiratory symptoms remained below 160 µg/m^3 8 hour average. This was also found for an asthma symptom score although only in asthmatics not on medication (Delfino et al., 1998). Schwartz et al. (1994) found a flattening of the relationship with lower respiratory symptoms <u>above</u> 80 µg/m^3 24 hour average but considered this implausible shape was due to confounding. The relationship for cough, after control for PM_{10}, was linear (p=0.31 in test for non-linearity). Thurston et al. (1997) (1 hour) and Ostro et al. (1993) (1 hour) also found linear relationships.

Several panel studies of lung function have used censoring of days above a certain concentration to investigate thresholds. Higgins et al. (1990) found no significant effect on lung function in children after removal of days above about 240 µg/m^3 1 hour average, although there are many studies which have shown effects on lung function below this level. Spektor et al. (1988) found a significant association with lung function in active children remained after removal of all days above 120 µg/m^3 1 hour average. Brunekreef et al. (1994) found that, in vigorously exercising cyclists, significant associations with lung function remained after removal of all days above 100 µg/m^3 1 hour average but became non-significant after removal of all days above 80 µg/m^3. Similarly, Brauer et al. (1996) found a significant association with lung function was maintained in active farm workers with removal of all days above 80 µg/m^3 1 hour average but not with removal of all days above 60 µg/m^3. It should be noted that censoring days above a certain concentration also involves reducing the total days in the analysis and thus a loss of statistical power. This may itself result in a loss of statistical significance.

Bergamaschi et al. (2001) found a linear relationship (R^2=0.484) between 2 hour average ozone in the range 60 to 220 µg/m^3 and changes in serum CC16 (a marker of increased epithelial permeability) in subjects with wild type NADPH quinone reductase and null glutathione-S-transferase μ_1. This was not found in subjects bearing other genotypes. (The former genotype is a proposed susceptible group in terms of oxidative stress). Correlations with decreased FEV_1 and the forced expiratory vital capacity (FVC) were also found mainly in this susceptible group. This genotype is present in 30% of the population. Other candidates for genetic susceptibility to ozone, from evidence in mice, include the tumour necrosis factor Tnf and toll-like receptor 4 Tlr4 gene (Kleeberger et al., 2001). In communities with the lowest ozone concentrations, variant TNF genotypes were associated with a higher risk of wheezing outcomes (Gilliland et al., 2003). Thus, there are indications that subjects with particular genotypes are responding to ozone at lower concentrations than the general population. This needs to be taken into account when considering thresholds.

Several studies have compared associations with ozone by season and often find greater associations in the summer when ozone levels are higher (e.g. Anderson et al., 1996; Simpson et al., 1997; Sunyer et al., 1996). This might appear to provide support for a threshold. However, the studies often divide the year into two six month periods for which the ozone concentrations overlap for the majority of the exposure range (e.g. Simpson et al 1997). In other studies (e.g. Sunyer et al., 1996 in Barcelona), the ozone range in winter/spring is no lower than the full year range in other places where significant associations have been found such as London (Anderson et al., 1996). Hoek et al. (1997) adjusted for TSP and did not find a greater association of all-cause mortality with 24 hour average ozone in the summer. In contrast, Moolgavkar et al. (1995) with a good contrast in 24 hour average ozone concentrations and adjustment for sulphur dioxide and TSP did find a greater association in the summer. The non-significant associations found in many studies in the cool season may be due to the different patterns of confounding by other pollutants, of personal exposure and of the chemistry of the polluted environment in different seasons, rather than to the small differences in ozone concentrations. Seasonal differences may therefore be less informative about thresholds than might be expected.

Another approach is to examine the results from places where ozone concentrations are low (<160 µg/m^3 8 hour average or <180 µg/m^3 1 hour average). Although not all studies show significant associations (Bremner et al., 1999; Zmirou et al., 1996; Hong et al., 1999), positive and significant associations with all-cause mortality have been found in Brisbane with a maximum ozone concentrations of 126 µg/m^3 8 hour average (Simpson et al., 1997), in Vancouver with maximum ozone concentration of 150 µg/m^3 1 hour average (Vedal et al., 2003) and in London with a maximum ozone concentration of 148 µg/m^3 8 hour average (Anderson et al., 1996). These associations were stable to adjustment for other pollutants.

Some studies have found positive and statistically significant associations with respiratory hospital admissions, for example, in Brisbane with a maximum 8 hour average concentration of 130 µg/m^3 (Petroeschevsky et al., 2001) and in London with a 95th percentile 8 hour average concentration of 74 µg/m^3 (Ponce de Leon et al., 1996). Another study in London with a maximum 8 hour average ozone concentration of 160 µg/m^3 was positive but not significant (Atkinson et al., 1999). A positive and significant association was found in a meta-analysis of results from 16 Canadian cities with a 99th percentile of 174 µg/m^3 1 hour average (Burnett et al., 1997).

Given the above results, it would be difficult to rule out the possibility of an association at ozone concentrations below 120 to 160 µg/m^3 8 hour average. In fact, if there was a threshold it could well be below this, as it is unlikely that a single day or a few days close to the maximum concentration would be sufficient to drive a significant association alone. The 90th percentiles in these studies (where given) are around 60 to 80 µg/m^3.

Studies of non-asthmatics in areas with maximum ozone concentrations up to 228 µg/m^3 1 hour average, 186 µg/m^3 8 hour average or 82 µg/m^3 24 hour average did not find statistically significant associations with lower respiratory symptoms (Hoek et al., 1999; Declercq et al., 2000; Hoek et al., 1995; Ward et al., 2002). The only exception was a study in vigorously exercising cyclists with a maximum 1 hour average ozone concentration of 196 µg/m^3 (Brunekreef et al., 1994). On the other hand, increases in asthma attacks have been found in severe asthmatics in Paris with a maximum ozone concentration of 86 µg/m^3 8 hour average (Desqueyroux et al., 2002).

Some studies found significant small negative effects on lung function in places where ozone levels did not rise above 140 or 160 µg/m^3 8 hour average (Korrick et al., 1998; Cuijpers et al., 1995). Rises in serum CC16, a marker of lung permeability, have been shown in cyclists at 2 hour average ozone concentrations of 120 or 160 µg/m^3 (Broeckhart et al., 2000).

Conclusions

Overall, it was not possible for all health outcomes to confidently define an unequivocal no-effect threshold for the whole population. For the reasons described above, interpretation of the shape of exposure-response relationships is very difficult to ascertain for ozone, particularly at the low end of the ambient range. However, in some studies associations with outcomes ranging from mortality to respiratory symptoms have been reported from locations where ozone never exceeds 120 to 160 µg/m^3 as 8 hour average values. Some panel studies suggest small effects on lung function above around 60 to 80 µg/m^3 1 hour average. Our confidence in the existence of associations with health outcomes decreases at concentrations well below these levels, as problems with negative correlations with other pollutants and lack of correlation with personal exposure increase, but we do not have the evidence to rule them out.

Further research

Clear conclusions concerning the shape of exposure-response relationships in epidemiological studies will always be difficult but, given the importance of this issue, we recommend further research to explore the shape of the exposure-response relationship for ozone. Greater understanding of the different factors which may influence the shape such as correlation with other pollutants, correlations with personal exposure and variations in the total oxidant burden of different polluted environments, may help. Recent work has increased understanding of possible genetic reasons for increased susceptibility to ozone, suggesting new types of susceptible groups, but the implications of this for the range of responses at different ozone concentrations have yet to be fully explored.

Particulate Matter:

Most epidemiological studies on large populations have been unable to identify a threshold concentration below which ambient PM has no effect on mortality and morbidity. It is likely that within any large human population, there is a wide range in susceptibility so that some subjects are at risk even at the low end of current concentrations.

Rationale:

After a thorough review of recent scientific evidence, a previous WHO Working Group concluded "If there is a threshold [for PM], it is within the lower band of currently observed PM concentrations in Europe" (WHO, 2003).

This was based on analyses of the large NMMAPS database (Daniels et al., 2000) on PM$_{10}$, on a simulation study (Schwartz & Zanobetti, 2000), and on a large Spanish study that investigated black smoke as PM indicator (Schwartz et al., 2001). Some methodological papers highlighting difficulties to pinpoint thresholds exactly on the basis of time series studies were also quoted (Zeger et al., 2000, 2001; Cakmak, 1999). Some smaller studies or studies using less appropriate PM metrics were not discussed in the previous document. These include a study that suggested that threshold concentrations of PM do exist. Smith (2000) re-analysed data from Birmingham, Alabama, and suggested that effects on (short-term) mortality were only evident at levels above ~80 µg/m^3 PM$_{10}$, i.e. above the 90th percentile of the distribution. The analysis was based on <4 years of observation, and <20 000 deaths. The authors also mentioned, however, that the analysis

could not exclude a threshold at a much lower level, below 20 µg/m^3 PM$_{10}$. Another analysis by the same authors (Smith et al., 2000) looked at data from Phoenix, on some 40 000 deaths occurring over a three-year period. This analysis suggested a threshold for PM$_{2.5}$ of about 20–25 µg/m^3 as a daily average. Both analyses had limited statistical power compared to some other studies such as Daniels et al. (2000) with a database of almost 3 000 000 deaths. Nicolich et al. (1999) re-analysed TSP data from Philadelphia and suggested that in these data, there was evidence for a threshold of about 125 µg/m^3 for the relation between daily average TSP and mortality. As no PM$_{10}$ or PM$_{2.5}$ data were available for comparison, this particular analysis has no applicability for identification of a threshold for PM$_{10}$ or PM$_{2.5}$ as observed in more concurrent studies.

A new simulation study by Brauer et al. (2002) has suggested that a threshold that exists on the individual level becomes obscured (i.e. invisible) on the (usually analysed) population level when the relationship between ambient and personal exposure is poor, but not when this correlation is reasonably high. Data were compared for PM$_{2.5}$, which had a relatively poor mean correlation coefficient between ambient and personal in the underlying dataset of 0.48, mean regression coefficient of 0.27 (s.d. 1.78) (Ebelt et al., 2000) and sulphate with a relatively high correlation between ambient and personal, with a mean correlation coefficient of 0.96, mean regression coefficient of 0.78 (s.d. 0.23). The implication of this simulation exercise is that a threshold that truly exists at the individual level is not likely to be missed in a study using ambient monitoring of a pollutant with reasonably high correlations between ambient and personal exposure. The database in the simulation exercise of Brauer et al. (2002) is interesting in the sense that it has a correlation between ambient and personal PM$_{2.5}$ that is rather lower than in most other studies of the issue.

The "threshold" issue has now also been directly looked at for PM$_{2.5}$ (Schwartz et al., 2002) in a large dataset from six cities, studied over 8–18 years, and including >400 000 deaths. A variety of approaches showed that the relationship between PM$_{2.5}$ and total mortality persisted down to very low levels (2 µg/m^3), with little evidence of a threshold. When, using source apportionment techniques, the PM was partitioned to various sources, "traffic" particles were found to be related to mortality, with no evidence of a threshold, after controlling for particles from other sources.

Another way of addressing the "threshold" issue is to investigate what the lowest range of exposure is over which significant associations between air pollution and health have been observed. This can be done by looking at the concentration range per se, but also by "censoring" the data to below a predefined cut point, effectively removing all data from the analysis above that cut point. A 1995 review (Brunekreef et al., 1995) has systematically reviewed the literature from this perspective up to that time. Effects of PM$_{10}$ on mortality were observed at less than 100 µg/m^3 (Pope et al., 1992, Dockery et al., 1992), and of PM$_{2.5}$ on symptom exacerbations at less than 75 µg/m^3 (Ostro et al., 1991). When effects are found over such ranges, a threshold, if it exists, must be considerably lower than the upper bound of the range, as it is highly unlikely that a significant relationship would be driven completely by just a few observations at the highest end of the exposure range. It is, of course, well known that "outliers" in any dataset can influence the shape and the statistical significance of an exposure response relationship; however the analyses quoted before which have used non parametric smoothing techniques, have not suggested steeper slopes at higher concentrations. In censored datasets, which by definition have removed all values above a certain concentration, it is virtually impossible that "outliers" would still exist that determine the shape and significance of the exposure response relationship.

With the advent of the more sophisticated analyses of threshold phenomena discussed earlier, it has become less important to use relatively crude approaches such as censoring. The argument remains valid, however, that studies conducted in low concentration areas provide some insight into the upper bounds of thresholds, if they exist. One recent example is a study from Vancouver by Vedal et al. (2003), which studied mortality in a period when the 90th percentile of 24 hour average PM_{10} was 23 µg/m^3, the maximum only 37 µg/m^3. Still, significant effects on mortality were found.

It seems that recent, statistically powerful studies that have looked for thresholds for PM_{10}, $PM_{2.5}$ and black smoke were unable to find one. As stated in the report on the January 2003 workshop in Bonn, epidemiological studies are unable to exactly define a threshold if there is one. The combined arguments provided in the previous paragraphs make it highly unlikely, however, that a threshold would exist at a level anywhere near the level of 35 µg/m^3 which has been put forward for consideration in the draft position paper on PM of the CAFE working group.

All of the above arguments refer to time series studies. There are only few studies on effects of long-term exposure of PM on mortality, and even fewer of these have examined the shape of the exposure response relationship. The most powerful study (Pope et al., 2002) used non parametric smoothing to address this issue, and found no indication of a threshold for $PM_{2.5}$ for either cardiopulmonary or lung cancer mortality, within the range of observed $PM_{2.5}$ concentrations of about 8–30 µg/m^3. Further modelling of these data suggested that the exposure response relationship for $PM_{2.5}$ was actually steeper in the low exposure range up to about 16 µg/m^3. In contrast, analyses for sulfates suggested that a threshold might exist at about 12 µg/m^3 (Abrahamowicz et al., 2003).

5.4 Contribution of different sources to PM-related health effects

> **Explanation provided by the European Commission to this question:**
> The WHO first report put a clear emphasis on the health effects of small PM originating from combustion sources. Can these relationships be quantified giving the source contribution to health effects? How may uncertainties in the source apportionment and the particle characterization (size and composition) influence the quantitative assessment of pinpointing a source as being the contributor to health effects? Also, is there information and associated uncertainty on the health effects of specific secondary particle mass, such as the particle mass fraction due to agriculture activities leading to ammonia containing particles?

Answer:

Only a few epidemiological studies have addressed source contributions specifically. These studies have suggested that combustion sources are particularly important.

Toxicology, because of its simpler models and potential to tightly control exposures, provides an opportunity to determine the relative toxic potency of components of the PM mix, in contrast to epidemiology. Such toxicology studies have highlighted the primary, combustion-derived particles having a high toxic potency. These are often rich in transition metals and organics, in addition to their relatively high surface area. By contrast, several other components of the PM mix are lower in toxic potency, e.g. ammonium salts, chlorides, sulphates, nitrates and wind-blown crustal dust such as silicate clays.

Despite these differences among constituents under laboratory conditions, it is currently not possible to precisely quantify the contributions from different sources and different PM components to health effects from exposure to ambient PM.

Rationale:

To date only a limited number of investigations have related health endpoints to specific particle components and/or source markers. Results from the Harvard Six Cities Study suggest that daily mortality was mostly associated with combustion sources such as traffic, coal and residual oil (Laden et al., 2000). This study looked at pollution data obtained in the 1980s when it was still possible to use lead as a reliable tracer for traffic exhaust. So, the results are relevant for a mixture of traffic-related air pollution for which lead is a tracer, and it cannot be stated with certainty that these results are still representative for current day mixtures. In addition, the Harvard group examined the heterogeneity of PM_{10} related health risks reported in the NMMAPS study which used data obtained largely during the 1990s (Janssen et al., 2002). Their findings showed that the PM_{10} related risk for hospital admissions due to cardiovascular disease increased with the fraction of PM_{10} originating from highway emissions. Similarly, the European APHEA study found that the slope of the PM and health relationship was higher in areas exhibiting relatively high NO_2 concentrations (Katsouyanni et al., 2001). These areas were mostly impacted by mobile sources providing evidence for an enhanced toxicity of PM emitted from these sources. Work conducted in the United States of America by Mar et al. (2000), using factor analysis, identified vehicle emissions, vegetative burning and regional sulphate as important predictors of cardiovascular mortality in Phoenix, Arizona. A similar analysis by Tsai et al. (2000) analysing three New Jersey cities, using data from the early 1980s, found motor vehicles, metal industry, sulphate and oil burning to contribute to mortality. Moreover, a study conducted in Amsterdam showed that the slope of mortality on black smoke was twice as high in subjects living in homes on the main road network (Roemer and van Wijnen, 2001; Roemer and van Wijnen, 2001). Black smoke, which is an important component of PM, was also shown to be twice as high on these roads, suggesting that traffic emissions contributed strongly to the PM associated mortality observed in Amsterdam. The recent Delfino et al. (2003) study from California found that effects of PM_{10} on asthma worsening were completely explained by elemental and organic carbon, which the authors attributed in large measure to diesel exhaust in the study region.

Although these studies on source-specific particle toxicity underscore the importance of combustion sources, especially traffic emissions, the data do not allow precise attribution of health effects to different sources. Source apportionment techniques need to be further developed, in step with emission databases, in order to make these types of estimates more precise. Nevertheless, the case for attributing significant health effects of air pollution to vehicle emissions is strong, also given the results of recent other studies documenting impaired health in subjects living close to busy roads (see question on hot spots).

PM is a complex mixture and if composition data is available it is, of necessity, unsophisticated. Epidemiology is therefore often poor at determining the role of composition in driving adverse health effects. By contrast, a primary aim of toxicology is the determination of the relative toxic potency of substances. This is generally accomplished by the use of animal models, cell systems and human chamber studies using short-term, well-controlled exposures. Components of the PM mix have been examined for toxic potency in a range of toxicology studies. These studies suggest that some of the components of PM that contribute substantially to the mass are low in toxic potency; these include salts such as nitrates, sulphates and chlorides (Schlesinger & Cassee,

2003) and wind-blown crustal dust including silicate clays; it should be noted, however, that some silicates are toxic (Hetland et al., 2001). Primary, carbon-centred, combustion-derived particles have been found to have considerable inflammogenic potency (Cassee et al., 2002) as a consequence of their high surface area or number (Donaldson et al, 2002), their organic (Marano et al., 2002) and metal (Costa and Dreher, 1997) content. In support of this contention, human subjects exposed by inhalation to high levels of diesel exhaust showed inflammation in lung biopsies (Salvi et al., 2000).

There is insufficient information about the relative toxicity of the particle mass fraction due to agriculture activities leading to ammonia containing particles, compared to particles originating from other sources.

5.5 Impact of methods of analysis used in epidemiological studies

> **Explanation provided by the European Commission to this question:**
> In the review of the guidelines a systematic assessment of the uncertainties (such as confidence intervals) of the relative risks would give a better understanding of the degree of uncertainty. This item should also include the uncertainty in the application of different models (including GAM).

Answer:

This answer addresses matters relating to uncertainties in methods of analysis used. Epidemiological studies use statistical models of various types, including Poisson and logistic regression. The estimates of effect provided by air pollution studies are generally accompanied by confidence intervals. These convey the precision of the estimate or statistical uncertainty that arises because the analyses are subject to a degree of random error. To a varying degree, the results of these analyses are sensitive to the details of the model and the specification of confounding and interacting factors. Extensive sensitivity analyses have shown that associations between air pollution and health remain irrespective of the methods of analyses used.

Rationale:

Uncertainty has implications both for identification of the possibility that air pollution is a hazard and for estimating the actual size of any effect for the purposes of risk estimation. CAFE has requested to consider a systematic assessment of uncertainty. This is in two parts: the first is statistical uncertainty and the other is model uncertainty.

1.   Statistical uncertainty
The reviewers were aware of the need to consider statistical uncertainty. In the material supplied for the review of time series studies, for example, all estimates were accompanied by 95% confidence intervals which indicate the precision of the estimate as well as the likelihood that it is due to chance. In some cases, where there are multiple comparisons, it has been prudent to adopt a more stringent level of statistical significance. Meta-analytic estimates such as from the APHEA study are also accompanied by confidence intervals. Thus, the possibility of an association being due to chance was taken into account. Similarly, all the cohort evidence reviewed was described in terms of a central estimate and 95% confidence intervals.

2.   Model uncertainty – time-series studies

Time-series analysis is complex, especially in the need to control for time-varying confounding factors. It is inevitable that different statistical approaches will lead to different results. Various studies in the past have looked at the sensitivity of results to different modelling strategies (Health Effects Institute, 1997; Samoli et al., 2001) and found that while the precise estimates vary between the statistical approaches used, the overall effects are still in favour of an adverse health effect.

This question was thrown into relief by the discovery of Dominici and colleagues that the results of the NMMAPS analyses were very sensitive to the criteria for convergence in the program (S Plus) that was used for the generalized additive modelling (GAM) approach, which was in vogue in the latter part of the 1990s (Dominici et al., 2002). In addition, other workers identified a problem with the underestimation of standard errors (Ramsey et al., 2003). Using the St. George's database, a comparison was made of GAM and non-GAM results in the published literature. The results are shown in Table 1. There was a tendency for GAM results to be higher than non-GAM results, though either method showed significant adverse effects.

Table 1. Summary estimates for studies of PM$_{10}$ and daily mortality by GAM or non-GAM statistical model and by single-city or multicity study design. % change in mortality per 10 μg/m^3 increase in PM$_{10}$

Studies	No. of estimates	Summary Estimate	95% CI
GAM			
All studies	172	0.60	(0.52, 0.68)
NMMAPS[2]	90	0.5	No numerical estimate[1]
APHEA 2 [3]	21	0.6	(0.4, 0.8)
Single city studies	61	0.68	(0.57, 0.79)
Single city studies (adjusted for publication bias)		0.6	(0.5, 0.8)
Non-GAM			
Single city studies	26	0.55	(0.38, 0.73)
Single city studies (adjusted for publication bias)		0.4	(0.2, 0.6)
All Studies (GAM and Non-GAM)	198	0.59	(0.52, 0.66)

Following this discovery, many investigators re-analysed their data using GAM models with stricter convergence criteria. The APHEA group found little change in the original estimates for mortality (Katsouyanni et al., 2002) and hospital admissions (Atkinson, letter in preparation to AJRCCM).

This question has now been thoroughly investigated and reported recently by the Health Effects Institute (2003). The approach was to compare the original GAM based estimates with those

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[1] No numerical estimate for 95% CI given. Graphical representation of marginal posterior distribution for PM$_{10}$ indicated that effect was very unlikely to be due to chance. Note that in the paper by Dominici et al. (2002), the pooled estimate using default convergence criteria is 0.41 (posterior standard error 0.05). We have chosen the estimate given in the earlier published report (Samet et al., 2000).

from GAM models using stricter convergence criteria, and with those using Generalized Linear Modelling (GLM) with natural cubic splines. CAFE is referred to this report for a fuller description of the findings of this re-analysis; in summary:

1.   for NMMAPS mortality, stricter convergence criteria and GLM methods resulted in lower estimates of effect (40–50% reduction), though these were still statistically significant;

2.   for hospital admissions, there were smaller reductions (8–19%) in the NMMAPS results when the revised methods were used;

3.   a variety of additional studies were re-analysed, including APHEA 2. These also tended to find smaller but still significant estimates, but less so than for NMMAPS. For some series, such as hospital admissions due to respiratory disease for the APHEA studies, the results were generally insensitive to stricter convergence criteria or to the use of GLM;

4.   important uncertainties remain as to what is the best model to use for this type of analysis.

3.   Model uncertainty – cohort studies

Model uncertainty has also been examined in cohort studies. A good example is the reanalysis of the ACS cohort study (Health Effects Institute, 2000). This involved a complete reanalysis using new statistical approaches, such as the incorporation of spatial correlation in the models. A wide range of sensitivity analyses was performed. The conclusion of this was that the original findings were robust in the sense that the estimates observed in the earlier analysis were substantiated in size and direction. However, the estimates did show sensitivity to the models used and interactions with various factors such as educational level. There was also uncertainty as to the relative importance of the main pollutants studied.

5.6 Possible regional characteristics modifying the effects of air pollution

Explanation provided by the European Commission to this question:
The assessment of the risks builds on a concentration response relationship based on a number of studies from the United States and Europe. However, different parts of Europe have different mixes of air pollution due to differences in sources, climate and so forth. To what extent may uncertainties of the applicability of these relations influence the risk assessment due to particles and other priority pollutants?

Answer:

Potentially this could be a very influential issue since the characteristics of populations, environments and pollution (including particle concentration, size distribution and composition) vary throughout Europe. However, at this stage there is not sufficient evidence to advocate different guidelines for particles or other priority pollutants in different parts of Europe.

Several studies on short and long-term effects of particulate matter have consistently reported an association between pollution levels and mortality; however, there are differences in the size of the estimated effects of PM according to geographical region or according to the levels of other variables (potential effect modifiers). For example, it has been reported that the short-term effects of PM_{10} are greater where long term average NO_2 concentration is higher, when the proportion of the elderly is larger and in warmer climates. Modification by socioeconomic factors, such as the level of education, has also been reported. Plausible explanations for some of these observations have been proposed.

Effect modification, for example by the age distribution in a population and by climate should, if possible, be taken into account in sensitivity analysis of health impact assessments or risk assessments.

Possible effect modifiers of other criteria pollutants have not been investigated to any extent so far.

Rationale:

In the context of several studies of the health effects of air pollution, the heterogeneity of effect estimates between cities or areas has been identified and investigated (Katsouyanni et al., 1997; 2001; Samet et al., 2000; Krewski et al., 2003; Levy et al., 2000). Thus, in the APHEA project it was first noted that the short-term effects of particles on mortality were lower in cities of central-eastern Europe (Katsouyanni et al., 1997). Similarly in the NMMAPS project the highest effects of particles were estimated for north-east United States (Samet et al., 2000). This issue was investigated further in the APHEA 2 project, where a number of variables (city characteristics) hypothesized to be potential effect modifiers, were recorded and tested in a hierarchical modelling approach (Katsouyanni et al., 2001). This led to the identification of several factors that can explain part of the observed heterogeneity. The following were the most important effect modifiers identified.

- Mean temperature. In warmer cities larger estimates of the effects of particles on mortality are found (e.g. 0.8% versus 0.3% increase in mortality per 10 $\mu g/m^3$ change in PM_{10}). We do not know the mechanism through which this is occurring. One possibility is that in warmer climates populations are more exposed to outdoor air pollution by spending more time outdoors (especially in the summer) or by keeping the indoor/outdoor air exchange rate higher. This is supported by the higher effects estimated during the warm season in several studies (Katsouyanni et al., 1997; Samet et al., 2000). It is also supported by the finding that lower indoor penetration of outdoor air (e.g. due to the higher prevalence of air conditioning) is associated with lower health effects (Janssen et al., 2002). Another possible explanation could focus on considerations of the particle mix in warmer compared to colder climates and especially on the proportion of primary and secondary particles or the influence of the hours of sunlight on photochemical reactions that produce larger concentrations of organic fine particles and increased oxidant capacity of the ambient pollutant mixture. In any case, this issue should be further investigated.

- NO_2 long-term average concentration. In cities with higher NO_2 levels the estimated effects were higher (e.g. 0.8% versus 0.2% increase in mortality per 10 $\mu g/m^3$ change in PM_{10}). This may reflect a real interaction between NO_2 and PM or it may indicate that high NO_2 levels imply larger proportions of particles originating from traffic. This latter explanation is supported by other findings, which suggest that traffic particles might be more toxic than those from other sources (Jannsen et al., 2002; Laden et al., 2000). Results from the NMMAPS project are also compatible (Samet et al., 2000).

- It is generally accepted that air pollution causes larger effects to members of sensitive population subgroups. There is evidence that the effects are larger among the elderly (Viegi G & T Sandstrom, 2003; Gouveia & Fletcher, 2000). In the APHEA 2 analyses it was found that in cities with higher age-standardized mortality and those with smaller proportion of elderly (>65 years) the estimated effects were lower (Katsouyanni et al., 2001). This finding is supported by the analysis of Levy et al. (2000).

In the re-analyses of the six-city and the American Cancer Society (ACS) cohort studies on long-term effects of air pollution on mortality, several socioeconomic variables have been tested as potential effect modifiers (Krewski et al., 2003). It was found that lower education was associated with higher relative risks of mortality among those exposed to higher ambient particle concentrations. The results of the Dutch cohort study are compatible with the findings of the ACS study (Hoek et al., 2002). In a short-term effect study, there was limited evidence of effect modification by social factors (Zanobetti et al., 2000, O'Neill et al., 2003).

Recently, the problems identified with the application of GAM models for the analyses of short-term effects of air pollution and especially the underestimation of the standard errors of the effect estimates, lead to the conclusion that heterogeneity has been overestimated in reported studies (Ramsay et al., 2003). However, the re-analyses indicates that the patterns of effect modification remain the same, although the contrast in the size of the estimates at various levels of the effect modifier is smaller (Health Effects Institute, 2003).

6. Are there specific population groups that should be brought into special attention?

> **Explanation provided by the European Commission to this question:**
> In the first report from WHO the effects on particular population groups is highlighted on several occasions. From the policy point of view it is important to have an understanding of the risks for the different groups (no single group would have to have unacceptable risks). WHO is invited to investigate the possibility to assess the sensitivity such groups and to assess the risks due to present air pollution levels for some important health endpoints, *inter alia* increased child mortality and asthma exacerbation due to exposure to PM and ozone.

Answer:[2]

A number of groups within the population have potentially increased vulnerability to the effects of exposure to air pollutants. These groups comprise those who are innately more susceptible to the effects of exposure to air pollutants than others, those who become more susceptible for example as a result of environmental or social factors or personal behaviour and those who are simply exposed to unusually large amounts of air pollutants. Members of the last group are vulnerable by virtue of exposure rather than as a result of personal susceptibility.

Groups with innate susceptibility include those with genetic predisposition that render them unusually sensitive, for example, to the broncho-constrictor effects of ozone or liable to produce an unusually marked inflammatory response on exposure to allergens. Very young children and unborn babies are also particularly sensitive to some pollutants.

Groups which develop increased sensitivity include the aged, those with cardio-respiratory disease or diabetes, those who are exposed to other toxic materials that add to or interact with air pollutants and those who are socioeconomically deprived. When compared with healthy people, those with respiratory disorders (such as asthma or chronic bronchitis) may react more strongly

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[2] NB: The WHO report "Health aspects of air pollution with particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2)" provides pollutant-specific information on this issue (WHO, 2003). In addition, WHO has launched a systematic review of the impact of air pollution on children's health. It is planned to publish this report in mid 2004.

to a given exposure both as a result of increased responsiveness to a specific dose and/or as a result of a larger internal dose of some pollutants than in normal individuals exposed to the same concentration of pollutants. Increased particle deposition and retention has been demonstrated in the airways of subjects suffering from obstructive lung diseases.

Lastly, those exposed to unusually large amounts of air pollutants perhaps as a result of living near a main road or spending long hours outdoors, may be vulnerable as result of their high exposure.

Introductory Remarks:

The fact that some individuals are more affected than others by exposure to air pollutants has been known since the early years of air pollution research. Studies of the London fog of 1952 revealed that the elderly and the very young were most affected (Ministry of Health, 1954). The analysis of causes of death suggested that those suffering from cardiorespiratory disease might have been especially sensitive to the mixture of particles and sulphur dioxide that characterised the London smog of the period. More recent work has confirmed this perception and has identified a considerable number of groups of individuals who are likely to be at special risk when exposed to air pollutants.

Concern about the impact of air pollution on children's health has also increased recently. The European Commission has invited WHO to complement the current review (the work led by the Scientific Advisory Committee) by an in-depth review of this topic. The leading topic of the Fourth Ministerial Conference on Environment and Health, Budapest 2004 is the effects of environmental factors on children's health: "The future for our children". WHO is organizing a systematic review and assessment of the issue. This systematic review should be regarded as separate from the current work which has sought, specifically, to answer the follow-up questions posed by CAFE.

In addition, the meta-analysis of time-series studies undertaken by experts at St George's Hospital Medical School in London, on behalf of WHO, has looked specifically at the effect of age on coefficients linking air pollutants and health endpoints. The results of this analysis will be available on http://www.euro.who.int/air.

The statement provided below is a summary of the thinking of the WHO working group and the Scientific Advisory Committee and does not purport to be a systematic review. To undertake such a review in all the areas mentioned below was not possible in the time available for this work.

The terms sensitivity, susceptibility and vulnerability are used, sometimes interchangeably and incorrectly, to describe a greater than expected response of an individual or group of individuals to air pollutants. We use the terms susceptibility and vulnerability as defined below. We have not used the term sensitivity.

Susceptibility: The likelihood of producing a significantly larger-than-average response to a specified exposure to air pollutants.

Vulnerability: The likelihood of being unusually severely affected by air pollutants either as a result of susceptibility to the effects of these substances or as a result of a greater than average exposure. "Susceptibility" is thus seen as a subset of "vulnerability".

Susceptibility
Susceptibility can be subdivided into innate and acquired susceptibility. Innate susceptibility may be due to genetic predisposition or to incomplete development of normal (adult) physiological functions. A young child may be susceptible to a given pollutant because detoxification processes are not yet fully developed. Such susceptibility is transient and disappears with age and growth. Acquired susceptibility may be due to disease, socioeconomic status or age. A number of mechanisms are known to play a part and are discussed below. It should be noted, however, that "socioeconomic status" is not a precise identification of a causal factor.

Vulnerability
In addition to the susceptible groups outlined above some individuals are vulnerable to the effects of air pollutants as a result of their greater than average exposure to these substances. Such exposure may be due to living near busy roads or spending long hours outdoors each day. It is important to distinguish clearly between vulnerability due to increased exposure and vulnerability due to innate or acquired susceptibility.

Innate susceptibility
(a)   Genetically predisposed
It has been known since 1991 that the unusual sensitivity of some strains of mice to ozone is due to mutations of the Inf locus on chromosome 9. Further work has shown that more than one gene may be involved and one allele may be responsible for the extreme sensitivity to ozone seen in some animals. Kleeberger et al. (1996) described the MdSOD gene on chromosome 17 and the Trifa (pro-inflammatory cytokine TNFα) gene, also on chromosome 17. Mice deficient in SOD (superoxide dismutase) show a greater than usual inflammatory response to ozone and higher levels of the cytokine IL-6 in bronchoalveolar lavage fluid. These studies show that genetic factors can, in animals, affect susceptibility to the effects of at least one classical air pollutant: ozone (Kleeberger et al., 1991; 1992; 1996; Carlsson et al., 1996).

Recent work in man has shown that abnormalities of the members of the glutathionine-S-transferase super family (GSTM$_1$, GSTT$_1$ and GSTP$_1$) can affect responses of children to oxidant air pollutants. Gilliland et al. (2004) have shown that individuals with the GSTM$_1$-null or GSTP$_1$ Ile105 wildtype genotypes produced an enhanced allergic response to diesel-exhaust particles. Individuals with GSTM$_1$-null genotype produced a larger than usual increase in conversion of IgE and histamine in nasal lavage fluid after challenge with allergen or diesel exhaust particles than individuals with the functional genotype. Hong et al. (2003) have shown that these polymorphisms are important in controlling neonatal vulnerability to maternal smoking. A further example is provided by the –308 promotor polymorphism of TNFα which has been shown to enhance the lung function response to sulphur dioxide in chamber studies (Winterton et al., 2001). Interestingly, polymorphisms of the TNFα gene have been shown to be associated with asthma. In communities with the lowest ozone concentrations, variant TNF genotypes were associated with a higher risk of wheezing outcomes (Witte et al., 2002; Gilliland et al., 2003).

A number of studies has focused on the possible effects of maternal exposure to air pollutants on fetal growth (birth weight), prematurity (gestational age at delivery) and the incidence of stillbirths. The studies reported between 1996 and 2001 have been reviewed by Glinianaia et al. (2004). The authors concluded that the evidence was compatible either with a small adverse effect of particulate air pollution on fetal growth and duration of pregnancy or with no effect. Recent work from the United States argued that over 70% of the overall reduction in infant

mortality during the first year of life could be attributed to the, on average, 15 µg/m^3 decline in TSP that occurred during the economic recession of 1981–1982 (Chay & Greenstone, 2003). A number of studies, for example, Bobak (2000) has reported associations between sulphur dioxide and low birth weight. Other studies have not found such effects. The general impression is that maternal exposure to air pollutants is related to decreased fetal growth and prematurity. An interesting implication of such a conclusion relates to the increased prevalence of asthma in children with low birth weight. Mortimer showed that asthmatic children who were born either before the thirty-seventh week of gestation or with a low birth weight (<2500 g) had a significantly increased risk of symptoms and a reduction in lung function in response to summertime air pollution in the eastern half of the United States (Mortimer et al., 2000).

Acquired susceptibility
There is convincing evidence that the elderly and those suffering from cardio-respiratory disorders are susceptible to the effects of air pollutants (Gordon & Reibman, 2000; Pope, 2000; Takafuji & Nakagawa, 2000; Donaldson et al., 2001). In addition, it has long been known that patients with asthma are more affected by exposure to irritant air pollutants such as sulphur dioxide than other individuals (Linn et al., 1983; Sheppard et al., 1981). A recent study has shown a differential sensitivity of patients with and without asthma exposed to diesel exhaust (Stenfors et al., 2004). The cytokine profile of lavage fluid was counter-intuitively found to contain more classical inflammatory cytokines in the non-asthmatic group. Earlier work had shown a more marked neutrophil response in asthmatic subjects (Scannell et al., 1996). It has also been shown that the inflammatory response induced by exposure to ozone is longer lasting in asthmatic subjects than in controls (Balmes et al., 1997; Frampton et al., 1997a; 1997b). Work by Zanobetti et al. (2000) has focused on subgroups of patients with cardio-respiratory disorders and showed that those with acute respiratory infections and with defects in the electrical control of heart rate and rhythm appeared to be at particular risk of adverse effects on exposure to particles measured as PM_{10}.

These effects may be in part explained by the greater instability or susceptibility to insult likely in disease states, for example, an already inflamed airway and also by the increased deposition of both fine and ultrafine particles known to occur in diseased lungs. Such enhanced deposition leads to what could be regarded as an increased internal dose of particles on exposure to a given concentration of particles (Kim & Kang, 1997; Brown et al., 2002).

Zanobetti & Schwartz (2001) have recently shown that patients with diabetes are of increased risk of admission to hospital for treatment of heart disease on exposure to raised concentrations of particles. The risk amongst diabetics was twice that in the non-diabetic population. The authors hypothesized that the possible links between exposure to particles and clotting factors might explain this effect, as diabetes itself is characterized by abnormalities in such factors. It is interesting that the authors pointed out that they had not found age to be a modifying factor of the effects of PM_{10} on hospital admissions for disorders of the heart and lungs (Zanobetti & Schwartz, 2001). Systematic analysis will be needed to clarify the possible effects of age on susceptibility to particulate air pollution.

Increased vulnerability due to increased exposure
A number of studies have shown increased effects associated with living near busy roads (Roemer & Wijnen, 2001; Janssen et al., 2003; Hoek et al., 2002). Children may also be exposed to a greater extent than adults because of their greater physical activity and likelihood that they spend a larger part of the day outdoors. The higher metabolic rate of children, revealed in a

higher minute volume per unit mass also increased the internal dose of pollutants for a given ambient concentration. This point applies also to athletes and others exercising outdoors.

7. What is the basis for maintaining the WHO NO$_2$ annual specific guideline value of 40 µg/m^3?

> **Explanation provided by the European Commission to this question:**
> The second edition of the WHO guidelines (published in 2000) stated that "selecting a well supported value based on the studies reviewed has not been possible" and the recent paper from WHO suggests there is no new evidence to support the selection of a numerical value. The answer to this question of the first set of questions on NO$_2$ to WHO concludes that there is no new evidence to warrant changing the current guideline. As it stands, a person who was not aware of the history might assume that the current guideline is robust and there is no evidence to change it. The current guideline is however based on limited evidence and there is no newer evidence to make it more robust. Consequently WHO should assess how confident it is in the current guideline.

Answer:

There is evidence from toxicological studies that long-term exposure to NO$_2$ at concentrations higher than current ambient concentrations has adverse effects.

Uncertainty remains over the significance of NO$_2$ as a pollutant with a direct impact on human health at current ambient air concentrations in the European Union, and there is still no firm basis for selecting a particular concentration as a long-term guideline for NO$_2$. NO$_2$ is an important constituent of combustion generated air pollution. In recent epidemiological studies of the effects of combustion-related (mainly traffic generated) air pollution, NO$_2$ has been associated with adverse health effects even when the annual average NO$_2$ concentration is within a range that includes 40 µg/m^3, the current guideline value. However, we are unable to establish an alternative NO$_2$ guideline from these studies. We therefore recommend that the WHO annual specific guideline value of 40 µg/m^3 should be retained or lowered.

Rationale:

The WHO Air Quality Guideline value of 40 µg/m^3 as annual mean was based on limited but suggestive evidence from indoor studies that long-term exposure to combustion products from indoor gas appliances including NO$_2$ had a deleterious effect on health. The figure of 40 µg/m^3 was adopted from the International Programme on Chemical Safety (IPCS; Environmental Health Criteria 188) and reflected the association between indoor exposure to combustion products from indoor gas appliances including NO$_2$ and lower respiratory tract illnesses in children. There was some uncertainty over the appropriate numerical value for the guideline, as NO$_2$ was not directly measured in all studies. It was also noted that outdoor epidemiological studies had shown associations between outdoor concentrations of NO$_2$ and small reductions in lung function and a slightly increased prevalence of asthma.

Since the current WHO Air Quality Guidelines were established (WHO, 2000) the evidence regarding the long-term effects of NO$_2$ as a single pollutant and adverse human health has increased a little. There is new evidence from human and animal studies in vivo (Pamanathan et al., 2003; Blombert et al., 1997; van Bree et al., 2000) and from limited in vitro (Devalia et al.,

1993; Bayram et al., 1999*)* studies that short-term exposure to NO_2 can be toxic to airway and alveolar epithelial cells. This is a result of its oxidant capacity to cause tissue damage (Persinger et al., 2002). This lends plausibility to the possibility that there could be long-term effects. There are no human studies of long-term exposure to pure NO_2; studies have only been performed with short-term exposure to concentrations higher than common ambient concentrations and not at the low levels that might be causing long-term effects (e.g. Chitano et al., 1995; Hyde et al., 1978; Wegmann et al., 2003). There are also studies showing lung damage following long-term exposure to nitrogen dioxide in animals. Again the concentrations used are above common ambient concentrations.

Epidemiological studies of short-term changes in NO_2 concentrations suggest that these may be associated with ill health at common ambient concentrations. This may have implications for long-term effects. None of these studies, however, provides a significantly improved basis for the long-term guideline of 40 µg/m^3 as annual average for NO_2 as a single toxic pollutant gas.

We have been asked to comment on our confidence in this guideline. Our reply is that it remains difficult to provide solid scientific support for the numerical value of the guideline. There still is no robust basis for setting an annual average guideline value for NO_2 through any direct toxic effect. However, new epidemiological evidence has emerged that increases our concern over health effects associated with outdoor air pollution mixtures that are apparently well characterized by NO_2. We refer to evidence supporting effects of a mixture of NO_2 and derived pollutants including nitrate rich particles and nitric acid vapour at mean NO_2 concentrations in a range that includes 40 µg/m^3 (range 8–75 µg/m^3) (McConnell et al., 2003). This study demonstrated an association between bronchitis symptoms among children with asthma and the yearly variability of NO_2 concentrations in southern Californian communities. We note that the highest 4 year average concentration of NO_2 in the communities studied was 75 µg/m^3. Of interest is the high correlation between NO_2 and Organic Carbon (OC) in this study (0.69). In two-pollutant models, adjusting for O_3, PM_{10}, $PM_{2.5}$, coarse particles, inorganic acid and elemental carbon, OC was the pollutant that retained most of its significance. $PM_{2.5}$ and NO_2 also had fairly robust associations with symptoms; $PM_{2.5}$, NO_2 and OC all lost their significance in all two-pollutant models including combinations of these, showing that either was representing a gas-particle mixture most likely dominated by traffic emissions. In the same study, Gauderman et al. (2000) reported an association between annual average PM_{10}, $PM_{2.5}$, inorganic acid and NO_2 concentrations and a reduction in lung growth in fourth grade children. In this study, the highest concentration of NO_2 recorded was about 45 ppb (80 µg/m^3) while in 6 of the 12 communities studied the annual average concentrations was less than 40 µg/m^3. Again, there were significant correlations between these pollutants (up to 0.87 for NO_2 and inorganic acid), and all of the associations lost significance in two-pollutant models including any combination between the four. A further study from this cohort (Gauderman et al., 2002) included more detailed measurements of acid vapours and of elemental and organic carbon. In this study acid vapour (sum of nitric, formic and acetic acid) was the clearest determinant of reduced lung function growth, and again, acid, NO_2 and particle metrics mostly lost significance in two-pollutant models. In this second study, however, NO_2 coefficients reduced less after adjustment for $PM_{2.5}$ or PM_{10} than vice versa. What these studies point towards is that NO_2 is serving as an indicator of a complex mixture, and that its indicator value is reduced, but not removed by adjustment for $PM_{2.5}$ and other particle metrics.

In Europe, a negative association between the development of lung function and ambient NO_2 concentrations (Schindler et al., 1998) has been reported, where the highest ambient annual mean

concentration of NO_2 in the communities studied was 57.5 µg/m^3. In this study, the role of co-pollutants was not examined

A recent series of European studies has used Geographic Information Systems (GIS) to generate exposure distributions for traffic-related pollutants, primarily NO_2, "soot" (measured as reflectance of particle filters) and $PM_{2.5}$. These studies were conducted over annual average NO_2 ranges of 25–84 µg/m^3 (Carr et al., 2002; Nicolai et al., 2003), 15–67 µg/m^3 (Hoek et al., 2001; Hoek et al., 2002), 27–44 µg/m^3 (Janssen et al., 2001; Janssen et al., 2003), 20–67 µg/m^3 (Gehring et al., 2002) and 13–58 µg/m^3 (Brauer et al., 2002). In all of these, the correlation between the two or three metrics of exposure was high, so that they could not be separated. In all studies, there were positive associations between NO_2 and health endpoints such as respiratory symptoms and mortality indicating that over these low ranges of exposure, NO_2 as marker of traffic-related pollution is clearly associated with adverse effects on health. In a European study of lung cancer, NO_2 (calculated from NO_x) was used explicitly as a marker of road traffic exhaust levels, since historical road maps and traffic flow estimates, and dispersion models, were used to map the road traffic contribution to ambient NO_2. These geographical estimates produced an individual average in the range 4–51 µg/m^3 for the first decade of the study (Bellander et al., 2001). In a similar recent European study total residential NO_x (mainly from vehicles) was historically assessed by dispersion modelling, showing a five year individual average in the range 1–170 µg/m^3 (Nafstad et al., 2003). Residential road traffic exhaust levels corresponding to over 30 µg/m^3 NO_2 or NO_x were found to increase the lung cancer risk by about 40% 10–30 years later in the two studies (Nyberg et al., 2000, Nafstad et al., 2003). A point worthy of note is that associations of ambient NO_2 concentrations with health effects is manifest in a much smaller geographical scale than has previously reported (Cohen, 2003).

The current annual average NO_2 guideline value of 40 µg/m^3 is within the exposure ranges reported in these investigations, and one being conducted almost entirely over a range below the current annual average guideline concentration value. These recently published studies document that NO_2, as marker of a complex mixture or traffic-related pollution, is consistently associated with adverse effects on health at relatively low levels of long-term average exposure. They also show that these associations cannot be completely explained by co-exposure to $PM_{2.5}$, but that other components in the mixture (such as organic carbon and acid vapour) might explain part of the association. As such components have not been routinely measured, and as there is much information on NO_2 concentrations in ambient air, it seems reasonable to propose to CAFE that a prudent annual average limit value for NO_2 be set, acknowledging that this takes account of any direct toxic effect that NO_2 might exert and to control complex mixtures of combustion-related pollution (mainly from road traffic).

There are some limitations to using NO_2 purely as an indicator for combustion-related air pollution, since the mixture will vary in different places and change with time. However, this limitation would also apply for, e.g. $PM_{2.5}$ since it is not known what aspects or components of particulate air pollution are responsible for the adverse health effects observed. When more information on the relationship between different aspects of combustion-related air pollution and health is available, it is possible that more efficient protection against the health effects of these complex gas-particle mixtures will be obtained by regulating another metric than NO_2 alone or in combination (Seaton & Dennekamp, 2003). Such candidates include black smoke, elemental and organic carbon, measures of acidity, NO_x and particulate number concentration.

Research should be undertaken to determine whether NO_2 at concentrations achieved in the outdoor environment, has any detectable toxicity on the human lung using a range of outcome measures. Research is also urgently needed to determine which aspects or components of combustion mixtures are responsible for the adverse health effects observed in epidemiological studies.

8.   What is the evidence for adverse effects of coarse particles?

Answer:

There are a large number of epidemiological studies showing that PM_{10} (which includes both fine and coarse particles) has adverse health effects. Although smaller in number, the existing studies on the fine particle fraction ($PM_{2.5}$) show that there are also health effects from this fraction. Only recently have investigators begun to separately address health effects of coarse particles ($PM_{10-2.5}$). There is limited evidence that coarse particles are associated independently of $PM_{2.5}$ with mortality in time series studies. One study has investigated the effect of long-term exposure to coarse particles on life expectancy without producing evidence of altered survival. There is evidence that coarse particles are independently associated with morbidity endpoints such as respiratory hospitalizations in time series studies. Considerations of particle dosimetry, chemistry and toxicology provide further evidence of adverse health effects of coarse PM. Therefore, there is sufficient concern about the health effects of coarse particles to justify their control.

Rationale:

Composition
The difference in size and chemical composition between the coarse and the fine fraction of PM is likely to result in differences in type of disease and severity of effect. On the other hand, particle formation can be a complex and dynamic process that depends upon atmospheric chemistry and agglomerative interactions between the different-sized particles present in the particle phase. Particle agglomerates that are large enough to be in the coarse fraction may contain many ultrafine particles and other constituents attached to them that originally arose in the ultrafine fraction. Results of one of the few published studies, in which coarse and fine PM where compared for their effects showed that on the equal mass basis, coarse and fine particles both produce pulmonary inflammation (Dick et al., 2003; Shi et al, 2003; Pozzi et al., 2003).

Toxicology
Whereas the epidemiological studies associate PM_{10} or $PM_{2.5}$ with health effects a rapidly increasing number of toxicological studies focus on the different size fractions within PM_{10}. Most of these studies apply either concentrators for inhalation studies or novel PM sampling techniques for in vitro or in vivo health effects studies.

Becker et al. (2002, 2003) studied the potency to induce inflammatory mediators of coarse, fine and ultrafine ambient PM. They observed the strongest effects in the coarse fraction, and found an absence of effect from ultrafine particles. The authors suggest that the effects are linked with the presence of microbial cell structures and endotoxins. In support of this, Schins et al. (in press) have investigated the inflammogenic potential of coarse (2.5–10µm) and fine (<2.5µm) PM from both a rural and an industrial location in Germany. Bronchoalveolar lavage (BAL) of rat lungs 18 hours after instillation with PM showed that, irrespective of the sampling location,

the coarse fraction of PM_{10} caused neutrophilic inflammation in rat lungs, while its fine counterpart did not. The rural sample of coarse PM also caused a significant increase in the TNF content as well as glutathione depletion in the BAL fluid. Endotoxin present of the coarse fraction was the most likely explanation of this effect.

Since broncho-constriction is a clear symptom in people with chronic obstructive pulmonary disease or asthma, and dosimetry models predict that the tracheobronchial airways are also target for PM deposition of particles >1 µm, a relationship might be present between coarse mode PM and bronchoconstriction. Dailey et al. (2002) also studied the effects of the three size fractions in airway epithelial cells. Interestingly, coarse and ultrafine mode PM induced stronger responses (cytokine production) then the fine mode, and again with the coarse mode PM was the most potent fraction. Li et al. (2002) described that coarse and fine mode particles collected in Downey, CA, produced different effects in an oxidative stress model. In addition, the effects of coarse mode particles were most effective when collected in the fall and winter. Both coarse and fine PM are able to generate OH radicals and to induce formation of 8-hydroxy-2'-deoxyguanosine in cultures of epithelial cells (Shi et al., 2003). Pozzi et al. (2003) showed in an in vitro assay that coarse and fine fraction PM were equally effective in causing releases of inflammatory mediators, and that these effects were much stronger compared with carbon black suggesting that the contaminants adsorbed on the particles may be responsible for the observed induction. Other studies focus on oxidative stress and the effects on red blood cells. These have shown that although haemolytic potential was greater for the fine particles than for the coarse particles in equal mass concentration, when data were expressed in terms of PM surface per volume unit of suspension, the two fractions did not show any significant hemolytic differences. (Diociaiuti et al., 2001).

Dosimetry

A substantial fraction of inhaled coarse particles is deposited in the airways or lungs. This fraction is substantially greater than for particles in the fine fraction (i.e. $0.1 < d_{ae} < 2.5$ µm, see Fig. 4). The difference in tracheobronchial and thoracic deposition fractions between children and adults increases with particle size and is significantly greater for children (ages of 0–15 years old) than for adults.

Few investigators have specifically addressed the particle lung doses from fine and coarse PM. Venkataraman & Kao (1999) showed that on a mass basis, the proportion of fine PM being deposited in the pulmonary region is three times larger than the proportion of coarse PM. The number dose to the pulmonary region, however, was five orders of magnitude higher for fine than for coarse PM. This indicates that if effects of PM would even partly related to particle number, the fine fraction completely dominates effects related to pulmonary deposition.

Fig. 4. Modelled deposition of particles in the human respiratory tract using the MPPD (Price et al., 2002) model[3].
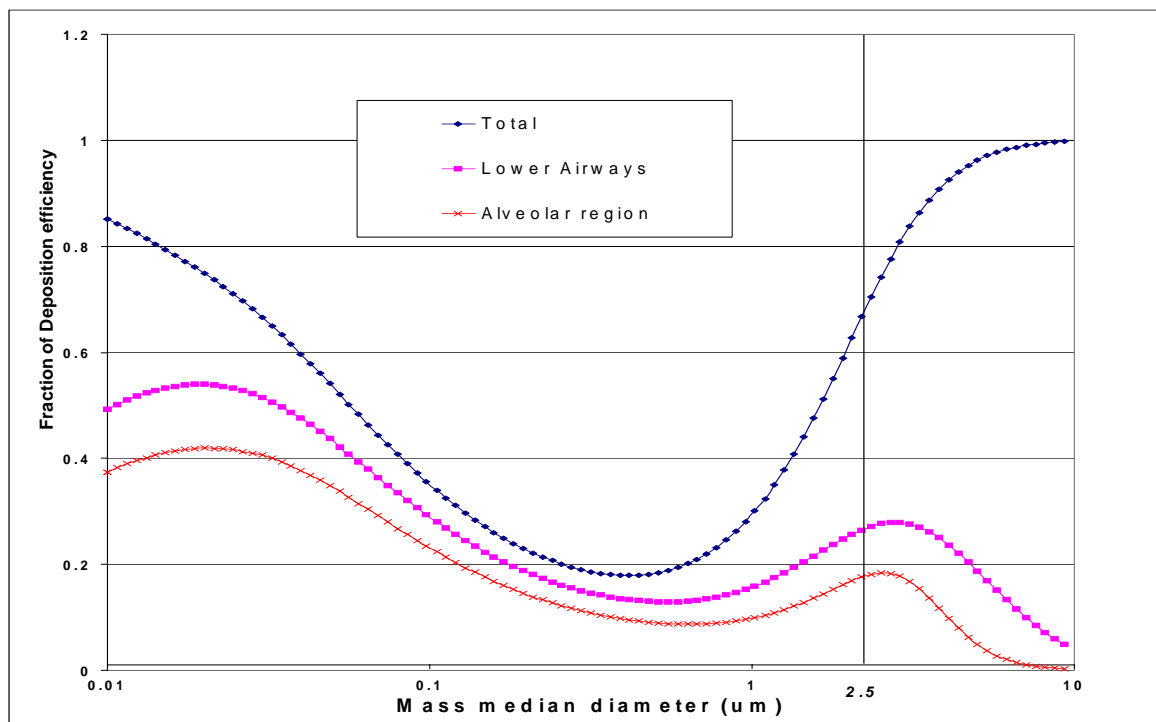
Epidemiology

In the last 15 years, airborne particles have been characterized in many epidemiologic studies by mass concentrations of particles smaller than 10 micrometer in diameter (PM_{10}), because particles of this size can penetrate into the thoracic part of the airways where they may have adverse effects. The more inclusive measure of "Total Suspended Particulates" (TSP) did incorporate larger particles, but was considered to be too unspecific to be used as a basis for air quality standards aimed at protecting human health. Because PM_{10} often to a large extent consists of particles smaller than a few micrometers, it cannot be easily distinguished in studies from fine particulate matter, often measured as particles smaller than 2.5 micrometers or $PM_{2.5}$. That is not to say that the concentrations are the same; the issue is that temporal and spatial variation of $PM_{2.5}$ and PM_{10} are often similar, despite the difference in sources and composition between fine and coarse particles, simply because $PM_{2.5}$ is often a large fraction of PM_{10}.

Only in recent years has the difference between coarse and fine particles come to be more explicitly appreciated in epidemiologic studies. Investigators have included separate measurements of fine and coarse particles in their studies rather than measurements of $PM_{2.5}$ and PM_{10}. This has shown that, in contrast to the high correlation between PM_{10} and $PM_{2.5}$, there is often much less correlation between $PM_{2.5}$ and coarse particles, usually defined and measured as particles larger than 2.5 and smaller than 10 micrometer. Of note is that sometimes this quantity is arrived at by subtracting a direct measurement of $PM_{2.5}$ from a direct measurement of PM_{10}; the disadvantage of this is that "coarse" particle measurement is then affected by two measurement errors rather than one. Other sampling configurations separate fine and coarse particles before they are collected on filters to be weighed, or detected by other means. These recent studies have made it possible to investigate the role of fine and coarse particles without running into the complication that any statement about PM_{10} is likely to be also valid for (or even

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[3] Settings: Default settings with nose-mouth breathing pattern.

dominated by) $PM_{2.5}$, simply because $PM_{2.5}$ is such a large fraction of PM_{10}. The observation that the correlation between "fine" and "coarse" particles is often low has made it relatively easy to separate their effects in field studies.

A detailed description of occurrence, measurement and correlations of coarse and fine particles can be found in Wilson & Suh (1997). These authors concluded that "fine and coarse particles are separate classes of pollutants and should be measured separately in research and epidemiologic studies. $PM_{2.5}$ and $PM_{(10-2.5)}$ are indicators or surrogates, but not measurements, of fine particles." To illustrate the last point, it has been shown that in certain areas windblown dust significantly contributes to $PM_{2.5}$ (Claiborn et al., 2000).

An early example of a study that addressed fine and coarse PM separately is a study from the United States of America (Schwartz et al., 1996) that found that daily mortality in six cities was associated with fine particles but not with coarse particles. Since then, a body of evidence has emerged that allows further analysis of the relative importance of fine and coarse particles. As there are virtually no studies that have defined "coarse particles" other than $PM_{10-2.5}$ (occasionally $PM_{15-2.5}$), what we know about "coarse mass" or CM refers to particles smaller than 10 (or 15) µm, and larger than 2.5 µm. The emphasis is on comparing effect estimates for fine and coarse particles within studies. First we try to answer the question whether there is evidence in recent time series studies of an effect of coarse particles on mortality, independent of effects of fine particles. These studies are ordered by number of observations because the larger the number of observations, the more informative a study is. Where available, the correlations between PM_{10} and $PM_{2.5}$, and between PM_{10} and coarse PM are also given. Some studies have addressed effects of coarse particles on morbidity endpoints. These will also be reviewed.

Effects of coarse particles on mortality
The results of time series studies on effects of fine and coarse particles on mortality are summarized in Table 2.

Six Cities study, United States of America
The original study by Schwartz et al. (1997) was essentially replicated by Klemm et al. (2000). This is still the study with the largest number of observations, around 190 000 deaths observed over a number of years in six towns in the United States of America. In this study, fine PM was associated with mortality but coarse PM was not. Of interest is that in the one town where CM was found to be associated with mortality (Steubenville), the correlation between FP and CM was high at 0.69. No two-pollutant analysis of these data has been reported.

Santiago, Chile
Cifuentes et al. (2000) analysed a large database from Santiago, Chile where PM levels where high. Both FP and CM were associated with mortality, but in a two-pollutant model containing both FP and CM, the association with FP was unchanged, whereas the association with CM all but disappeared.

Philadelphia, United States of America
Lipfert et al. (2000) re-analysed data from Philadelphia and surrounding areas, and found associations between mortality and fine and coarse PM of roughly similar magnitude, although the associations with CM were mostly not significant. The paper contains a large number of estimates without standard errors or confidence intervals, the denominator of which is given as "means minus 4th percentile"; there are various means, but no 4th percentiles reported. The

Environment Protection Agency's fourth draft version of the PM criteria document has calculated effect estimates which are in the order of a 1.6% increase in cardiovascular mortality per 10 µg/m^3 for both metrics, being significant for fine but not for coarse PM (US EPA, 2003).

Eight cities, Canada
In a study conducted in eight Canadian cities, Burnett et al. (2000; 2003) found both fine and coarse PM to be associated with mortality; no attempt was made to adjust these associations for each other. The effect estimates in the table are from the recent re-analysis report (Burnett et al., 2003). That report contains a variety of estimates, which show fairly similar estimates for fine and coarse mass in the range of 0.6 to 1.5 % increase in mortality for each 10 µg/m^3 increase in particle mass. The correlations between PM$_{10}$ and PM$_{2.5}$ and coarse mass respectively were much higher than the correlation between fine and coarse PM.

Santa Clara County, California, United States of America
Fairley et al. (1999; 2003) analysed a small number of deaths in Santa Clara County, California, and found mortality to be associated with fine but not coarse particles. The effect estimates in the table are from re-analysed data, using "new GLM". The correlations between PM$_{10}$ and PM$_{2.5}$ and coarse mass respectively were much higher than the correlation between fine and coarse PM.

West Midlands Conurbation, United Kingdom
A study from the United Kingdom by Anderson et al. (2001) found no association between mortality and either fine or coarse PM. However, in season-specific analyses there was a significant association with fine but not coarse PM in the warm season. The correlations between PM$_{10}$ and PM$_{2.5}$ and coarse mass respectively were much higher than the correlation between fine and coarse PM.

Mexico City, Mexico
Castillejos et al. (2000) analysed three years of mortality in a section of Mexico City where coarse PM measurements were available. Both fine and coarse mass were associated with mortality, but in a two-pollutant model, coarse mass was clearly dominant. The authors speculated that there was much biogenic contamination in the coarse mass fraction.

Wayne County, Michigan, United States of America
In a small study in Wayne County conducted over the 1992–1994 period, fine and coarse PM were both not significantly associated with mortality. The effect estimate for coarse mass was somewhat larger than for fine mass (Lippmann et al., 2000; Ito et al., 2003). As was found in other investigations, the correlations between PM$_{10}$ and PM$_{2.5}$ and coarse mass respectively were much higher than the correlation between fine and coarse PM.

Coachella Valley, California, United States of America
In a study conducted in the arid Coachella Valley, Ostro et al. (2000, 2003) found evidence for effects of fine particles (but not coarse particles) on total mortality. When the analysis was restricted to cardiovascular mortality, there was a significant association with coarse but not fine particles, although the effect estimate for fine particles was still much larger than for coarse PM. The results were generally unaffected by model specification (Ostro et al., 2003). In the re-analysis published in 2003, the authors looked at cardiovascular mortality only, so that no comparison is possible with the original report with respect to total mortality. Again, correlations between PM$_{10}$ and fine and coarse mass respectively were higher than the correlation between fine and coarse PM.

Phoenix, Arizona, United States of America
In a small study from Phoenix, Arizona, where coarse PM is higher than fine PM due to arid conditions, both were found to be associated with cardiovascular mortality at lag 0 (Mar et al., 2000, 2003). At lag 1 the association was stronger for fine (7.1% per 10 µg/m^3, 95% confidence intervals: 1.1–12.9%) than for coarse particles (1.6% per 10 µg/m^3, 95% confidence intervals: 0.5–3.8%). Again, correlations between PM_{10} and fine and coarse mass respectively were higher than the correlation between fine and coarse PM.

Another small study over a one year period in Atlanta has been reported (Klemm et al., 2000), with about 8400 deaths, showing no effect whatsoever although coefficient and t-statistic (t=1.15) for fine PM were larger than for coarse PM (t=0.21).

Schwartz analysed a time series of mortality data from Spokane, Washington where dust storm regularly occur. He found that on dust storm days (which had an average PM_{10} concentration of 263 µg/m^3), there was no increased mortality compared to control days which had an average PM_{10} concentration of 42 µg/m^3 (Schwartz et al., 1999).

The American Cancer Society (ACS) cohort study conducted in the United States found no evidence that coarse PM was associated with mortality over long periods of follow-up (Pope et al., 2002). This is an important observation because the health impact assessments within CAFE and the proposed annual average limit values for fine PM rely in part on the mortality effects seen in this and some other cohort studies.

Conclusion on coarse PM and mortality
There is some evidence for effects of coarse PM on mortality. This is most clear in studies from arid regions (Phoenix, Coachella Valley, Mexico City) where PM concentrations are relatively high. Studies from the Detroit area and from Canada also provide some support for an effect of coarse PM on mortality. Few studies have analysed fine and coarse PM *jointly*. Two studies that did so (from Santiago, Chile, and Santa Clara County, California) showed that effects of coarse PM completely disappeared after adjustment for fine PM. In both studies, the effects of fine PM remained after adjustment for coarse PM. One study from Mexico City found the opposite: coarse PM effects remained, but fine PM effects did not. The correlation between fine and coarse PM in all of these studies was moderate at values between 0.28 and 0.59 with one higher value at 0.69 in Steubenville. In contrast, the correlations between PM_{10} and fine as well as coarse PM was much larger in all studies. Usually, correlations between PM_{10} and fine PM were largest, but there were some exceptions, notably from arid areas where PM_{10} was dominated by coarse PM. The implication is that analyses based on PM_{10} are generally unable to support statements on the relative importance of fine and coarse PM. The modest correlations between fine and coarse PM on the other hand do allow separation of the two effects. It is unfortunate that so far, all but a few studies have failed to report the results of two-pollutant analyses.

There is only one report from Europe at this point. This study from the United Kingdom found no effect of either fine or coarse PM on mortality. However, in the warm season, significant effects of fine but not coarse PM were observed.

The ACS cohort study did not show an effect of spatial variations in coarse particles on mortality.

Effects of coarse particles on morbidity
A study of respiratory hospital admissions from Washington State (Schwartz, 1996) found an association with PM_{10}. This association which was not significantly smaller in the autumn period when PM_{10} was suggested to be dominated by wind blown dust. One would expect a smaller association if wind blown dust was innocuous. A more recent study from the same area found that asthma hospital admissions were associated with fine as well as coarse particles, which were only moderately correlated at 0.43 (Sheppard et al., 1999).

A study from Anchorage, where PM_{10} is dominated by coarse crustal material, found significant effects of PM_{10} on outpatient visits for asthma, bronchitis and upper respiratory tract infections (Gordian et al., 1996).

Another study from Washington State found a small increase in respiratory hospital admissions after dust storms during which maximum 24 hour PM_{10} concentrations exceeded 1000 µg/m^3 (Hefflin, 1994). Coefficients were estimated to be about 3–4% per 100 µg/m^3, which is not very different from coefficients estimated from large time series studies on PM and hospital admissions.

In a study among school children (Schwartz & Neas, 2000), fine particles were found to be associated with reduced peak flow and increased lower respiratory symptoms. Independently, coarse particles were only associated with increased cough, which was attributed to the irritative potential of coarse particles in the respiratory tract.

In a recent study from Toronto, asthma hospitalizations among 6–12-year-old children were found to be associated with coarse particles more strongly than with fine particles (Lin et al., 2002).

Analyses conducted within the Children's Health Study in southern California found no evidence of an association between coarse PM and bronchitic symptoms in a prospective assessment of children with asthma (McConnell et al., 2003). In the same study, NO_2 and organic carbon were the pollutants most closely associated with symptoms. The correlation between annual average $PM_{2.5}$ and coarse particles was only 0.24, whereas PM_{10} was highly correlated with both at 0.79. This analysis took into account both within and between community variations over a four year period. This illustrates that separate assessment of associations with fine and coarse PM is possible when both are actually measured. Earlier publications from this cohort found some evidence of an effect of coarse PM on lung function growth that was inseparable from effects of other particle metrics (Gauderman et al., 2000, 2002). However, in these analyses the within-community variation in air pollution exposures over time was not taken into account, and correlations between PM_{10}, coarse and fine particles were much higher for this reason than in the analysis of bronchitic symptoms among children. In areas of Europe where roads are being sanded, and studded tyres are used in winter, episodes of high so-called "spring dust" concentrations occur when the snow melts. One study from Finland has addressed possible health consequences (Tiittanen et al., 1999). TSP, PM_{10} and $PM_{2.5}$ were measured, and coarse mass was estimated by subtracting $PM_{2.5}$ from PM_{10}. Median concentrations were 57, 28, 15 and 8 µg/m^3 respectively, but maximum concentrations were 234, 122, 55 and 67 µg/m^3 (24 hour average). Correlations between the different particle metrics were very high at 0.90–0.98 in this study so that they could not be separated in the analysis. Morning peak flow and cough were found to be associated with all of these particle metrics (except TSP which was not analysed) in

a panel of asthmatic children. Because of the high correlations between metrics, no firm conclusions with respect to an independent role of coarse PM can be drawn.

In the time series study from the United Kingdom quoted earlier (Anderson et al., 2001), none of the particle metrics analysed had a clear relationship with respiratory and cardiovascular hospital admissions.

A study from eight districts in four cities in China reported that the prevalence of respiratory symptoms in children was more strongly associated with TSP, and with coarse than with fine particles. Mean concentrations were high at 356 $\mu g/m^3$ for TSP, and 151, 92 and 59 $\mu g/m^3$ for PM_{10}, $PM_{2.5}$ and coarse mass respectively (Zhang et al., 2002).

Conclusion on coarse PM and morbidity

A few studies have found associations between respiratory morbidity endpoints and coarse particles in areas where no such associations with mortality were found. Evidence suggests that the irritative potential of coarse particles might be sufficient to cause respiratory morbidity leading to increases in hospital admissions. Some of these studies were conducted in areas where coarse PM is low, e.g. Seattle where the median and 90th percentile of the CM distribution were 14 and 29 $\mu g/m^3$ respectively (Sheppard et al., 1999).

The number of time series studies that have addressed effects of coarse PM seems too limited at the moment to allow derivation of exposure-response relationships. The sparse data reported show that effect estimates were sometimes of the same order as those for fine PM. Application of two-pollutant analyses in databases from which this has not yet been reported is urgently needed to address the question whether effects of coarse PM remain after adjustment for fine PM.

Very few data exist that allow estimates of long term effects of coarse PM on morbidity. One study from China, conducted at high levels of exposure, suggests that the prevalence of respiratory disease among children is especially associated with coarse PM.

Table 2. Summary of time series studies relating coarse particulate matter to mortality

Reference	Location	Approx. # of events	Measurement of $PM_{10-2.5}$	Concentrations in $\mu g/m^3$	R fine-coarse	R PM_{10}-fine	R PM_{10}-coarse	Effect estimates per 10 $\mu g/m^3$	Estimates from 2-pollutant model
Schwartz et al., 1996; Klemm et al., 2000	6 US cities	190 000	direct	FP: 11.2–29.6 CM: 6.6–16.1	0.23–0.69	N/A	N/A	FP: 1.5 (1.1–1.9) CM: 0.4 (-0.1–1.0)	N/A
Cifuentes et al., 2000	Santiago, Chile	186 000	direct	FP: 58.3 CM: 46.4	0.52	N/A	N/A	FP: 0.7 (t=6.7) CM: 1.1 (t=4.9)	FP: 0.7 (t=4.7) CM: 0.1 (t=0.5)
Lipfert et al., 2000	Philadelphia	135 000	direct	FP: 17.3 CM: 6.8	N/A	N/A	N/A	FP: mostly significant CM: mostly insignificant	N/A
Burnett et al., 2000; 2003	8 Canadian cities	110 000	direct	FP: 13.3 CM: 12.6	0.37	0.84	0.81	FP: 1.4 (t=3.14) CM: 0.8 (t=2.04)	N/A
Fairley et al., 1999; 2003	Santa Clara County, CA	60 000	direct	FP: 13 CM: 11	0.51	0.85	0.65	FP: 2.9 (0.6–5.3) CM: 1.3 (-2.2–4.9)	FP 3.5 (0.7–6.6) CM -2.4 (-9.0–4.8)
Anderson et al., 2001	UK West Midlands	49 000	direct	FP: 14.5 CM: 9.0	0.34	0.92	0.56	FP: 0.3 (-0.8–1.5) CM: -0.5 (-3.8–2.0)	N/A
Castillejos et al., 2000	Mexico City	28 000	indirect	FP: 27.4 CM: 17.2	0.52	0.89	0.84	FP: 1.5 (-0.0–3.0) CM: 4.1 (2.5–5.7)	FP: 0.2 (-1.7–2.1) CM: 4.0 (2.0–6.0)
Lippmann et al., 2000; Ito, 2003	Detroit Michigan County	25 000	direct	FP: 15 CM: 12	0.42	0.90	0.72	FP: 0.8 (-0.6–2.4) CM: 1.1 (-0.9–3.3)	N/A
Ostro et al., 2000; 2003	Coachella Valley	21 000	indirect	FP: 16.8 CM: 30.5	0.28–0.46	0.46–0.68	0.94–0.97	Total mortality: FP: 4.4 (0.0–8.9) CM: 0.5 (-0.5–1.0) CVD mortality: FP: 3.3 (-2.2–10.0) CM: 1.0 (0.5–2.0)	N/A
Mar et al., 2000; 2003	Phoenix	4 200	indirect	FP: 13; CM: 34	0.59	0.77	0.97	FP: 3.5 (-0.1–9.4) CM: 2.7 (0.5–6.0)	N/A

9. What other aspects of air pollution are important to address in the development of air pollution policy in Europe?

> **Explanation provided by the European Commission to this question[4]:**
> Although the guidelines were revised as late as in 1997, or slightly later for dioxins, more recent research results or interpretation of earlier findings may influence European air pollution policies. Examples would be new information on the health effects and risks of heavy metals (Pt, such as Pd, Rh, Hg, Cd, Ni, Cr, As) and POPs (such as dioxins, PCBs) making it necessary to review and revise the present guidelines at a later stage. It is also important to have some information from the WHO on outstanding new findings – if any – on air pollution health effects likely to influence the European air quality policies.

The main purpose of this survey was therefore to identify any important issues related to health effects of air pollution in Europe, which are currently not adequately addressed by WHO Air Quality Guidelines and/or the European Commission's Clean Air for Europe programme.

Based on advice by the SAC, WHO decided to conduct a small survey among a wide range of experts to get additional views on this item. Experts were invited to highlight important aspects that are currently not addressed adequately in the development of air pollution policy in Europe. In agreement with the header under which this question was received *("On substances and pollutants that have not yet been addressed"),* it was mentioned that this could be linked to pollutants or exposure situations posing risk to health in Europe and not covered by the present regulations, or those for which new scientific information warrants re-evaluation of the available risk assessment. A copy of the letter that was sent to the experts can be found in Annex 3.

Roughly 10% of the experts that were contacted replied. Pollutants highlighted by experts include the following.

- The "classical" air pollutants carbon monoxide and sulphur dioxide. As a justification, it was indicated that new epidemiological studies revealed an association of these pollutants with severe health effects, which are not necessarily adequately reflected in the current WHO Air Quality Guidelines for Europe.

- Persistent organic pollutants (POP) such as PAH. For example, a recent assessment (United Kingdom Committee on Carcinogenicity, 2003) of the contribution of dibenzo[al]pyrene to the overall carcinogenic potential of PAH has caused concern about this substance. Dioxins, nitro-PAH and nitro-oxy-PAH were also mentioned.

- Heavy metals, in particular lead and some transitional metals. Lead was of concern since there are new studies suggesting effects at low concentrations.

- Carcinogenic volatile organic species 1.3-butadiene and benzene

- Nitrogen trichloride, since there is evidence of health effects from this substance from epidemiological studies.

Few experts suggested to assess the health effects from diesel versus gasoline exhaust emissions.

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[4] It should be noted that this question was provided by the Commission with the following heading: "*On substances and pollutants that have not yet been addressed in the CAFE programme that are/could be of concern for the systematic review by WHO.*"

The Working Group has also pointed out the unresolved issue of the combined effects of urban air pollution mix and its combined effects on health.

10. Concluding remarks

The working group agrees on the following general statements in response to the questions by the European Commission.

- The body of evidence on health effects of air pollution at levels currently common in Europe has strengthened considerably over the past few years; both epidemiological evidence and toxicological evidence has contributed to this strengthening; the latter provides new insights into possible mechanisms for the hazardous effects of air pollutants on human health and complements the large body of epidemiological evidence.

- The evidence is sufficient to recommend strongly further policy action to reduce levels of air pollutants including PM, NO_2 and ozone; it is reasonable to assume that a reduction of air pollution will lead to considerable health benefits.

- The present assessment represents the state-of-the-art understanding of the existing science. Further substantial reduction of the existing uncertainty will only be achieved by further targeted research and its subsequent systematic evaluation. The working group requests the European Commission and national funding authorities to make the necessary resources available to ensure that the outstanding questions can be addressed effectively to continuously support the political process of reducing the impact of environmental factors on human health.

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Annex 1

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[5] Not present at the WG meeting.

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Annex 2

GUIDING POINTS TO REVIEWERS OF "ANSWERS TO CAFE FOLLOW-UP QUESTIONS"

1. The documents provide short answers to a set of questions on specific aspects of air quality and health. The questions were received from the Clean Air For Europe (CAFE) secretariat of the European Commission.

2. Authors were selected based on recommendations of the Scientific Advisory Committee (SAC) of the project. Authors were instructed to provide short and clear answers; this is a prerequisite to be useful for the policy process within CAFE. Each answer is supported by a more comprehensive rationale. For some of the questions, selected experts in the field provided background documents in advance.

3. The answers were discussed by the SAC of the review project and revised, as appropriate, taking into account the advice of the SAC.

4. The answers and the rationales are not necessarily full reviews of the literature. Rather, they highlight recent studies that were *influential* in determining our views on the subject under consideration.

5. This review is complementary to the previous review completed in early 2003 (http://www.euro.who.int/document/e79097.pdf) and should not repeat this recent effort. It focuses[6] on the pollutants PM, O_3 and NO_2. This was a deliberate choice to focus only on those substances that are high on the European regulatory agenda at the moment, determined by the request of the EC CAFE programme to the WHO.

6. First and foremost, the reviewers are asked to judge the validity and clarity of the answers to the questions, and in particular:

   a) Has the recent research been correctly interpreted?

   b) Have influential papers been overlooked?

   c) Is a different answer more appropriate? If so, could the reviewer indicate *where* the more appropriate answer would be different?

The reviewers are asked to refrain from listing unquoted studies (there are many), *unless* they would change the answers that were given. The exception to this rule is for unquoted studies that, even though they do not change the answers, provide better support for those answers than the studies that were quoted.

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[6] Except Question 5, which was dealt with using a survey approach.

Annex 3

COVER LETTER OF SURVEY ON CAFE FOLLOW-UP QUESTION FIVE

Dear colleagues,

WHO is currently conducting a systematic review on health aspects of air quality in Europe to provide the **Clean Air for Europe** (CAFE) Programme (http://europa.eu.int/ comm/environment/air/cafe/index.htm) of the European Commission with relevant information on these issues. At the earlier stages of this review, most emphasis was given on three priority pollutants – particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2) – since advice on these pollutants is urgently required for further developing the strategy within CAFE. A report summarizing the main findings of this review has been published on WHO web page (http://www.euro.who.int/document/e79097.pdf). This part of the review was focused on specific questions, which were received from the CAFE Secretariat in advance.

In a follow-up, WHO received additional questions from the CAFE Secretariat. These questions request additional information on the priority pollutants. In addition, the following question is asked:

On substances and pollutants that have not yet been addressed in the CAFE programme that are/could be of concern for the systematic review by WHO

Q5. What other aspects of air pollution are important to address in the development of air pollution policy in Europe?
*Rationale for Q5. Although the (*WHO air quality*) guidelines were revised as late as in 1997, or slightly later for dioxins, more recent research results or interpretation of earlier findings may influence European air pollution policies. Examples would be new information on the health effects and risks of heavy metals (Pt, such as Pd, Rh, Hg, Cd, Ni, Cr, As) and POPs (such as dioxins, PCBs) making it necessary to review and revise the present guidelines at a later stage. It is also important to have some information from the WHO on outstanding new findings – if any – on air pollution health effects likely to influence the European air quality policies.*

WHO has decided to conduct a small survey among selected experts to get additional views on this important topic.

Therefore, you are kindly invited to provide your assessment on the mentioned issue.

One starting point for answering the question should be the knowledge on health effects as summarized in recent reports like the WHO Air quality Guidelines for Europe (WHO, 2000), or the assessment of health risk from POPs from long range transboundary air pollution (WHO, 2003). Please bear also in mind that the European Commission has also recently finalized its own risk assessment on health effects from PAH (see position paper on PAH available on: http://europa.eu.int/comm/environment/air/ambient.htm) and several metals (Ni, As and Cd; and on Hg; the corresponding position papers are also available on the above mentioned web page). The findings of these papers have been the basis for drafting the so-called fourth daughter

directive (which is expected to be presented by the European Commission in the next couple of months) to the air quality framework directive (96/62/EC).

If you feel that there are some important aspects which are currently not addressed adequately in the development of air pollution policy in Europe, please provide this information. You might indicate the pollutants or exposure situations posing risk to health in Europe not covered by the present regulations, or those for which new scientific information warrants re-evaluation of the available risk assessment. We would also appreciate to receive a justification for this assessment – this might be new findings published in scientific journals, or the results of a risk assessment performed at a regional or national level, or other sources of information – including references, as appropriate.

An answer to this survey before 1 June 2003 is highly appreciated. If you provide no answer until this date, we assume that there are no additional urgent topics to be considered by WHO in its systematic review.

We will keep you informed on the outcome of this survey.

Many thanks in advance!

Best regards,

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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