Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide

Report on a WHO Working Group

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ABSTRACT

Detailed knowledge on the effects of air pollutants on human health is a prerequisite for the development of effective policies to reduce the adverse impact of ambient air pollution. The second edition of WHO's Air quality guidelines (AQG) for Europe, formulated in 1996, summarizes systematically the effects of several air pollutants. These guidelines have been used extensively to establish regulatory frameworks for air quality assessment and management. To support the development of European Union policy on clean air for Europe (CAFÉ), this WHO Working Group (WG) was convened to review systematically the most recent scientific evidence on the adverse health effects of particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2). The review focused on studies that were published after the second edition of the WHO AQG was produced, and which have been influential in changing our views on health-related aspects of the substances under consideration. The WG adopted a recommendation to use fine particulate matter, ($PM_{2.5}$), as the indicator for health effects induced by particulate pollution such as increased risk of mortality in Europe, to supplement the commonly used PM_{10} (which includes fine and coarse particles). It also acknowledged the evidence that ozone produces short-term effects on mortality and respiratory morbidity, even at the low ozone concentrations experienced in many cities in Europe. Based on these findings the WG recommended that WHO should update exposure-response relationships for the most severe health outcomes induced by particulate matter and ozone presented by AQGs. The WG also concluded that an update of the current WHO AQG for nitrogen dioxide, which is also an important precursor for the formation of ozone and particulate matter, was not warranted.

Keywords

OZONE – adverse effects
NITROGEN DIOXIDE – adverse effects
AIR POLLUTANTS, ENVIRONMENTAL – adverse effects
META-ANALYSIS
AIR – standards
GUIDELINES

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1 Introduction

In most countries in Europe, ambient air quality has improved considerably in the last few decades. However, there is a large body of evidence suggesting that exposure to air pollution, even at the levels commonly achieved nowadays in European countries, leads to adverse health effects. In particular, exposure to pollutants such as particulate matter and ozone has been found to be associated with increases in hospital admissions for cardiovascular and respiratory disease and mortality in many cities in Europe and other continents. Recent studies have also tried to quantify the health effects caused by ambient air pollution; e.g., within the "Global Burden of Disease" project of the World Health Organization (WHO) it has been estimated that worldwide, close to 6.4 million years of healthy life are lost due to long-term exposure to ambient particulate matter (1, 2).

In the 1990s, WHO updated its Air quality guidelines (AQG) for Europe (3), to provide detailed information on the adverse effects of exposure to different air pollutants on human health. The prime aim of these guidelines was to provide a basis for protecting human health from effects of air pollution. The guidelines were in particular intended to provide information and guidance for authorities to make risk management decisions. The European Union (EU) used the WHO guidelines as a basis to set binding air quality limit values and target values for all EU member states for several pollutants (OJ L 163 from 29/06/1999; OJ L 313 from 13/12/2000; OJ L 067 from 09/03/2002).

2 Scope and Purpose

Since the most recent update of the WHO AQGs (3), there have been many new studies published that have investigated the effects of air pollution on human health. In order to provide (European) policy makers with state-of-the-art knowledge on the effects of air pollution on human health, it was considered necessary to review the new evidence systematically. At this stage, the review concentrated on the following pollutants: particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2). In particular, the question under discussion was whether there was sufficient new evidence to reconsider the current WHO guidelines.

3 Process

In 2001, WHO agreed with the European Commission to provide the Clean Air For Europe (CAFÉ) 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 available on WHO's website: http://www.euro.who.int/eprise/main/WHO/Progs/AIQ/Activities/20020530_1. 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.

The CAFÉ Steering Group, which advises DG Environment of the European Commission on the strategic direction of the CAFÉ programme, has formulated specific questions to be addressed by the WHO process; the questions indicate the scope of the review process and input required from WHO. In addition, three pollutants with the highest priority were selected: particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3). These questions were forwarded to WHO and then restructured by the SAC to enable a harmonized approach to be taken for the review of all three pollutants. The questions formulated by SAC are:

1. Is there new scientific evidence for WHO reconsideration of current WHO guidelines for the pollutant?
2. Which effects can be expected from long-term exposure to levels of the pollutant observed currently in Europe (both pre-clinical and clinical effects)?
3. Is there a threshold below which no effects of the pollutant on health are expected to occur in all people?
4. Are effects of the pollutant dependent upon the subjects' characteristics such as age, gender, underlying disease, smoking status, atopy, education, etc.? What are the critical characteristics?
5. To what extent is mortality being accelerated by long and short-term exposure to the pollutant (harvesting)?
6. Is the considered pollutant per se responsible for effects on health?
7. For PM: which of the physical and chemical characteristics of particulate air pollution are responsible for health effects?
8. What is the evidence of synergy / interaction of the pollutant with other air pollutants?
9. What is the relationship between ambient levels and personal exposure to the pollutant over short-term and long-term (including exposures indoors)? Can the differences influence the result of studies?
10. Which are the critical sources of the pollutant responsible for health effects?
11. Have positive impacts on public health of reduction of emissions and/or ambient concentrations of the pollutant been shown?
12. What averaging period (time pattern) is the most relevant from the point of view of public health? Would additional protection be provided by setting standards for more than one averaging period for the pollutant?

The SAC also proposed the details of the methodology and timetable of the review of health effects of PM, NO_2, and O_3, taking into account the guidelines provided in the WHO document "Evaluation and use of epidemiological evidence for environmental health risk assessment" (http://www.euro.who.int/air/Publications/20020621_9). Following a proposal from the SAC, WHO invited designated Centres of Excellence (CEs) to review the recent scientific evidence and to prepare (separate) background documents focusing on the epidemiological and toxicological evidence for the health effects of these pollutants.

Centres of Excellence and their primary responsibilities; (the centres which acted as main authors of the background papers are marked with *):

- Basel University, Switzerland (epidemiology of NO_2);
- Catholic University, Louwen, Belgium (toxicology of NO_2 and O_3);

- Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover, Germany (toxicology of PM);*
- IMIM, Barcelona, Spain (epidemiology of O_3);*
- Institut für Unweltmedizinische Forschung, Düsseldorf, Germany (toxicology of PM);
- Institute of Occupational Medicine, Edinburgh, United Kingdom (epidemiology of PM);
- Napier University, Edinburgh, United Kingdom (toxicology of PM);
- New York University School of Medicine, Tuxedo, United States of America (toxicology of NO_2 and O_3);
- RIVM, Bilthoven, Netherlands (epidemiology of PM);
- GSF- National Research Centre for Environment and Health, Institute of Epidemiology, Neuherberg/München, Germany (epidemiology of PM).*

The CEs met once to agree on the organization of the review and preparation of the background papers (The PM group met in Dusseldorf on 7 June 2002 and NO_2 & O_3 group in London, 28 June 2002). For further exchange of information, telephone and email connections were used.

The review also made use of a comprehensive bibliographic database developed at the St George's Hospital Medical School, London, according to the WHO guiding document "Evaluation and use of epidemiological evidence for environmental health risk assessment". The database was used to derive information on the magnitude of effects reported in numerous peer-reviewed publications for different health endpoints. A more detailed description of the database and its use can be found in Annex 2.

Based on the background documents prepared by the CEs, members of SAC drafted succinct answers supported by a justification (a rationale including references) using the most certain and most relevant scientific evidence. These answers reflected current state-of-the-art knowledge and are based on the most recent scientific findings, as well as accumulated foundation of evidence on these pollutants.

The drafts were discussed and revised at the third meeting of the SAC on 12 November 2002 and were subsequently sent out for a thorough scientific review. The reviewers were recommended by the SAC, which sought to recruit individuals who were knowledgeable about the relevant scientific fields. 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 asked to focus on the adequacy of coverage of the scientific evidence used in the papers and on the validity of the scientific evaluation. All comments received from reviewers were collected by WHO and distributed to the members of the WHO WG to allow analysis of the comments. The WHO WG discussed the papers and the comments at the meeting held from 13 to 15 January 2003 in Bonn, Germany. The list of members of the WG 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 WG:

- agreed on the text of each of the answers;

- provided guidance in regard to revisions of the rationale and the most appropriate supporting papers;
- indicated that an additional text on issues relevant for all three pollutants should precede the answers to the pollutants-specific questions;
- recommended specific follow-up activities to WHO.

A final draft of the report was once again sent out to all WG members for approval.

4 Issues relevant for all three pollutants

This section sets out the WG's views on core issues embedded within the questions.

The questions as framed, implicitly make assumptions that exposure to air pollution may carry a risk of adverse health effects. The request to review health effects of O_3, PM and NO_2 suggests that each has adverse effects on health per se, although the questions acknowledge the fact that people are exposed to a mixture of these pollutants and that there is the possibility of interactions among these three and other pollutants. These interactions might range from antagonistic to synergistic.

4.1 Sources of information

In carrying out the review, the WG faced the challenge of considering a remarkably large body of new evidence since the prior review. For particulate matter especially, there have been thousands of new papers addressing exposure, and providing new toxicological and epidemiological findings on adverse health effects. The new evidence is more limited on ozone and there is relatively little new evidence on NO_2. By necessity, the reviewers were selective, focusing on the most significant and relevant studies and upon meta-analyses when available.

The group's judgement relied primarily on the peer-reviewed literature as well as on the collective expertise of the group. The literature represented a variety of papers with different sources of information, including observational epidemiology, controlled human exposures to pollutants, animal toxicology, and in vitro mechanistic studies. Each of these approaches has strengths and weaknesses. Epidemiology is valuable because it generally deals with the full spectrum of susceptibility in human populations. Children, the elderly, and individuals with pre-existing disease are usually included. In fact, the effects in such susceptible groups may dominate the health outcomes reported. In addition, exposure occurs under real life conditions. Extrapolation across species and to different levels of exposure is not required. Sensitive methodologies, such as time series analysis, allow the identification of even small increases in overall mortality. However, the exposures are complex in epidemiological studies e.g., observational epidemiology, unless it is a study in the workplace, inevitably includes mixtures of gases and particles (4). By contrast, in controlled human exposures, the exposure can be to a single agent that can be carefully generated and characterized and the nature of the subjects can be rigorously selected and defined. Yet such studies are limited because they generally deal with short-term mild, reversible alterations and a small number of individuals exposed to single pollutants and do not include those with severe disease who may be at most risk of adverse effects.

Animal studies have the same strengths of well-characterized exposures and more uniform responding subjects. Invasive mechanistic studies can be carried out. More profound toxic

effects can be produced in animals than in experimental human studies. However, other limitations occur such as possible species differences and the frequent necessity of extrapolating from the higher levels used in animal studies to lower (and more relevant) ambient concentrations.

For these reasons, the best synthesis incorporates different sources of information. Therefore, this review did not rely solely on (new) epidemiological evidence, but included also new findings from toxicological and clinical studies.

4.2 Reconsideration of guidelines

"Is there new scientific evidence that indicates the need for WHO to reconsider the current WHO guidelines?" is the first of the twelve questions. The WG thoroughly evaluated the scientific literature since the second edition of the WHO Air quality guidelines for Europe was adopted (3) and explored whether new evidence justified reconsideration of the current WHO AQG. A positive answer is an indicator of a gain in knowledge with a reduction of uncertainty. While there are formal systems for assessing gains in knowledge, the WG relied on its collective expert judgment to determine if there was sufficient new evidence. Considerations in interpreting the evidence included:

- Identification of new adverse health outcomes
- Consistent findings of associations at lower levels than previously
- Enhanced mechanistic understanding leading to a reduction of uncertainty.

The WG noted that reconsideration does not necessarily imply that a change in the existing WHO AQG was considered warranted. When recommending reconsideration, the WG also did not necessarily take a position on whether a current standard based on the AQGs is appropriate or whether its form should be changed.

4.3 Thresholds

Question No. 3 ("Is there a threshold below which no effects of the pollutant on health is expected to occur in all people?") asks whether the evidence supports the concept of thresholds, *i.e.*, concentrations below which effects are not observed either in the general population or in selected susceptible populations of specific concern for particular pollutants. The presence of a threshold implies that a specific guidelines value could be set at a level below which safety could be assured and a margin of safety incorporated into setting the level of the standard. In the absence of a threshold, evidence of exposure-risk or concentration–risk relationships are needed to identify levels for standards that provide an acceptable level of risk; for a more detailed discussion see also *Use of guidelines in protecting public health* in: Air quality guidelines for Europe (3).

In responding to the question on thresholds, the WG noted the following:

- Increasingly sensitive epidemiological study designs have identified adverse effects from air pollution at increasingly lower levels.
- Thresholds differ depending on the outcome selected. Any threshold is a function of the endpoint chosen (death, diminished pulmonary function, or molecular changes), the nature

of the responding population (from the most healthy to the most ill), as well as the time at which the response is measured (immediate vs. delayed or accumulated).

- For some pollutants and adverse health effects, the population distribution of susceptibility may be such that effects are expected at low levels, even where current air quality standards are being met.
- Observational (epidemiological) studies have limited statistical power for characterizing thresholds. Toxicological studies are similarly limited.
- A lack of evidence for a health effect should not be interpreted as implying a lack of effect. ("Absence of evidence is not the same as evidence of absence".)
- It is worth considering replacing the threshold concept with a more complete exposure risk function.

While (no effect) thresholds may sometimes be useful, they represent a single point. In general, the working group feels that complete exposure/concentration – response relationships for different health endpoints provide more useful information for designing effective strategies to reduce adverse effects on human health.

4.4 Pollution Mixtures

The CAFÉ questions also address the independence of the effects of the three pollutants, acknowledging the possibility of combined effects such as synergism. The three pollutants are linked by complex atmospheric chemistry. The working group recognizes that air pollution exists as a complex mixture and that effects attributed to O_3, NO_2, or PM may be influenced by the underlying toxicity of the full mixture of all air pollutants.

Also, various sources such as automobiles or power plants emit mixtures. These pollutants are further transformed by processes in the atmosphere. For example, ground level ozone is a secondary pollutant produced by the interaction of sunlight with nitrogen dioxide and volatile organic compounds. Temperature and humidity are also important. Multiple components interact to alter the composition and as a result the toxicity of the mixture. Multiple components may also elicit diverse biological responses**.** However, only a small number of parameters is usually measured to characterize the mixture; these parameters are then used as indicators in epidemiological studies. The lack of availability of monitoring data sometimes impairs the possibility to identify the most relevant indicator for different health endpoints.

The independent effects of different pollutants must be teased apart by analytic methods in epidemiological studies; experimental design rarely permits the direct characterization of particular pollutants, e.g., for NO_2, it is not feasible to assess with any certainty whether the pollutant per se has adverse respiratory effects at ambient levels, since NO_2 may also be an indicator of traffic emissions. In addition, NO_2 and other nitrogen oxides also contribute to the generation of ozone and other oxidant pollutants and are a precursor of the formation of nitric acid and subsequently the nitrate component of PM. Thus, NO_2 is both a pollutant of concern and a surrogate for other concerns. The WG recognized these complexities in its interpretation of the evidence on NO_2.

4.5 Interactions

The terminology and methods used to characterize the combined effects of two or more pollutants or other hazards have been poorly standardized with substantial blurring of concepts derived from toxicology, biostatistics, and epidemiology (5, 6). Epidemiologists usually refer to *effect modification* if effects of multiple agents are interdependent while toxicologists assess whether the effects of multiple agents are *synergistic* (positive interdependence) or *antagonistic* (negative interdependence). Statisticians test whether there is *interaction* between independent determinants of certain risks. Effect modification is of interest because of its implications for preventing adverse effects and for insights provided into mechanisms of effects. Effect modification also has potential implications for prevention: synergism may increase the disease burden beyond that anticipated from the risk of one pollutant alone and could place some people at particularly high risk.

4.6 Critical sources of pollution

Question 10 ("Which are the critical sources of the pollutant responsible for health effects?") focuses on critical sources of the three pollutants. The answers are based on the group's knowledge of health effects and their relationship to particular sources of particles and gases. However, a rigorous answer to this question requires expertise relating to physical and chemical characteristics of emissions, their atmospheric transport and transformation, and thus complex atmospheric chemistry. The working group felt that a detailed evaluation of the relative importance and especially the spatial distribution of critical primary sources was outside its core competency.

5 Particulate matter (PM)

5.1 Introduction

Airborne particulate matter represents a complex mixture of organic and inorganic substances. Mass and composition in urban environments tend to be divided into two principal groups: coarse particles and fine particles. The barrier between these two fractions of particles usually lies between 1 μm and 2.5 μm. However, the limit between coarse and fine particles is sometimes fixed by convention at 2.5 μm in aerodynamic diameter ($PM_{2.5}$) for measurement purposes. The smaller particles contain the secondarily formed aerosols (gas-to-particle conversion), combustion particles and recondensed organic and metal vapours. The larger particles usually contain earth crust materials and fugitive dust from roads and industries. The fine fraction contains most of the acidity (hydrogen ion) and mutagenic activity of particulate matter, although in fog some coarse acid droplets are also present. Whereas most of the mass is usually in the fine mode (particles between 100 nm and 2.5 μm), the largest number of particles is found in the very small sizes, less than 100 nm. As anticipated from the relationship of particle volume with mass, these so-called ultrafine particles often contribute only a few % to the mass, at the same time contributing to over 90% of the numbers.

Particulate air pollution is a mixture of solid, liquid or solid and liquid particles suspended in the air. These suspended particles vary in size, composition and origin. It is convenient to classify particles by their aerodynamic properties because: (a) these properties govern the transport and removal of particles from the air; (b) they also govern their deposition within the respiratory system and (c) they are associated with the chemical composition and sources of particles. These properties are conveniently summarized by the aerodynamic diameter, that is the size of a unit-

density sphere with the same aerodynamic characteristics. Particles are sampled and described on the basis of their aerodynamic diameter, usually called simply the particle size.

The size of suspended particles in the atmosphere varies over four orders of magnitude, from a few nanometres to tens of micrometres. The largest particles, called the coarse fraction (or mode), are mechanically produced by the break-up of larger solid particles. These particles can include wind-blown dust from agricultural processes, uncovered soil, unpaved roads or mining operations. Traffic produces road dust and air turbulence that can stir up road dust. Near coasts, evaporation of sea spray can produce large particles. Pollen grains, mould spores, and plant and insect parts are all in this larger size range. The amount of energy required to break these particles into smaller sizes increases as the size decreases, which effectively establishes a lower limit for the production of these coarse particles of approximately 1 μm. Smaller particles, called the fine fraction or mode, are largely formed from gases. The smallest particles, less than 0.1 μm, are formed by nucleation, that is, condensation of low-vapour-pressure substances formed by high-temperature vaporization or by chemical reactions in the atmosphere to form new particles (nuclei). Four major classes of sources with equilibrium pressures low enough to form nuclei mode particles can yield particulate matter: heavy metals (vaporized during combustion), elemental carbon (from short C molecules generated by combustion), organic carbon and sulfates and nitrates. Particles in this nucleation range or mode grow by coagulation, that is, the combination of two or more particles to form a larger particle, or by condensation, that is, condensation of gas or vapour molecules on the surface of existing particles. Coagulation is most efficient for large numbers of particles, and condensation is most efficient for large surface areas. Therefore the efficiency of both coagulation and condensation decreases as particle size increases, which effectively produces an upper limit such that particles do not grow by these processes beyond approximately 1 μm. Thus particles tend to "accumulate" between 0.1 and 1 μm, the so-called accumulation range.

Sub micrometre-sized particles can be produced by the condensation of metals or organic compounds that are vaporized in high-temperature combustion processes. They can also be produced by condensation of gases that have been converted in atmospheric reactions to low-vapour-pressure substances. For example, sulphur dioxide is oxidized in the atmosphere to form sulphuric acid (H_2SO_4), which can be neutralized by NH_3 to form ammonium sulfate. Nitrogen dioxide (NO_2) is oxidized to nitric acid (HNO_3), which in turn can react with ammonia (NH_3) to form ammonium nitrate (NH_4NO_3). The particles produced by the intermediate reactions of gases in the atmosphere are called *secondary particles.* Secondary sulphate and nitrate particles are usually the dominant component of fine particles. Combustion of fossil fuels such as coal, oil and petrol can produce coarse particles from the release of non-combustible materials, i.e. fly ash, fine particles from the condensation of materials vaporized during combustion, and secondary particles through the atmospheric reactions of sulphur oxides and nitrogen oxides initially released as gases.

Recently a comprehensive report on PM phenomology in Europe was compiled (7). Sulfate and organic matter are the two main contributors to the annual average PM_{10} and $PM_{2.5}$ mass concentrations, except at kerbside sites where mineral dust (including trace elements) is also a main contributor to PM_{10}. On days when $PM_{10} > 50$ μg/m^3, nitrate becomes also a main contributors to PM_{10} and $PM_{2.5}$. Black carbon contributes 5–10% to $PM_{2.5}$ and somewhat less to PM_{10} at all sites, including the natural background sites. Its contribution increases to 15–20% at some of the kerbside sites.
Because of its complexity and the importance of particle size in determining exposure and human dose, numerous terms are used to describe particulate matter. Some are derived from and defined by sampling and/or analytic methods, e.g. "suspended particulate matter", "total suspended particulates", "black smoke". Others refer more to the site of deposition in the

respiratory tract, e.g. “inhalable particles”, which pass into the upper airways (nose and mouth), and “thoracic particles”, which deposit within the lower respiratory tract, and “respirable particles”, which penetrate to the gas-exchange region of the lungs. Other terms, such as “PM_{10}”, have both physiological and sampling connotations.

5.2 Answers and rationales

1) Is there new scientific evidence to justify reconsideration of the current WHO Guidelines for the pollutant?

Answer:

The current WHO Air quality guidelines (AQC) provide exposure-response relationships describing the relation between ambient PM and various health endpoints. No specific guideline value was proposed as it was felt that a threshold could not be identified below which no adverse effects on health occurred. In recent years, a large body of new scientific evidence has emerged that has strengthened the link between ambient PM exposure and health effects (especially cardiovascular effects), justifying reconsideration of the current WHO PM Air quality guidelines and the underlying exposure-response relationships.

The present information shows that fine particles (commonly measured as $PM_{2.5}$) are strongly associated with mortality and other endpoints such as hospitalization for cardio-pulmonary disease, so that it is recommended that Air quality guidelines for $PM_{2.5}$ be further developed. Revision of the PM_{10} WHO AQGs and continuation of PM_{10} measurement is indicated for public health protection. A smaller body of evidence suggests that coarse mass (particles between 2.5 and 10 μm) also has some effects on health, so a separate guideline for coarse mass may be warranted. The value of black smoke as an indicator for traffic-related air pollution should also be re-evaluated.

Rationale:
In 1996, the last US air quality criteria document on particulate matter was published and in the same year the reviews of the literature for the revised version of the WHO Air quality guidelines for Europe were finished, although the document was published only recently, in the year 2000 (3). At the time, WHO decided not to propose an AQG for PM as it was not possible to identify maximum long-term and/or short-term average concentrations protecting public health through exposure-response relationships based on the notion that a threshold below which no effect on health was expected.

Since then a large number of new epidemiological studies on nearly all aspects of exposure and health effects of PM have been completed. These have added greatly to the available knowledge, and therefore reconsideration of the current WHO AQG (3) is justified. The United States Environment Protection Agency has compiled the recent literature in a new Criteria Document that is currently still being reviewed and finalized (8).

Long-term studies

Specifically, the database on long-term effects of PM on mortality has been expanded by three new cohort studies, an extension of the American Cancer Society (ACS) cohort study, and a thorough re-analysis of the original Six Cities and ACS cohort study papers by the Health Effects Institute (HEI) (9, 10, 11, 12, 13). In view of the extensive scrutiny that was applied in the HEI reanalysis to the Harvard Six Cities Study and the ACS study, it is reasonable to attach most weight to these two. The HEI re-analysis has largely corroborated the findings of the original two US cohort studies, which both showed an increase in mortality with an increase in fine PM and sulfate. The increase in mortality was mostly related to increased cardiovascular mortality. A major concern remaining was that spatial clustering of air pollution and health data in the ACS study made it difficult to disentangle air pollution effects from those of spatial auto-correlation of health data per se. The extension of the ACS study found for all causes, cardiopulmonary and lung cancer deaths statistically significant increases of relative risks for $PM_{2.5}$. TSP and coarse particles (PM_{15} – $PM_{2.5}$) were not significantly associated with mortality (13). The effect estimates remained largely unchanged even after taking spatial auto-correlation into account.

Another concern was about the role of SO_2. Inclusion of SO_2 in multi-pollutant models decreased PM effect estimates considerably in the re-analysis, suggesting that there was an additional role for SO_2 or for pollutants spatially co-varying with it. This issue was not further addressed in the extension of the ACS study. The HEI re-analysis report concluded that the spatial adjustment might have over-adjusted the estimated effect for regional pollutants such as fine particles and sulphate compared to effect estimates for more local pollutants such as SO_2.

The Adventist Health and Smog (AHSMOG) study (9) found significant effects of PM_{10} on non-malignant respiratory deaths in men and women, and on lung cancer mortality in men in a relatively small sample of non-smoking Seventh-Day Adventists. Results for PM_{10} were insensitive to adjustment for co-pollutants. In contrast to the Six Cities and ACS studies, no association with cardiovascular deaths was found. For the first 10 years of the 15-year follow-up period, PM_{10} was estimated from TSP measurements which were much less related to mortality in the other two cohorts also. A later analysis of the AHSMOG study suggested that effects became stronger when analysed in relation to $PM_{2.5}$ estimated from airport visibility data (14), which further reduces the degree of discrepancy with the other two cohort studies. The US-EPRI-Washington University Veterans' Cohort Mortality Study used a prospective cohort of up to 70 000 middle-aged men (51 +/-12 years) assembled by the Veterans Administration (VA) (11). No consistent effects of PM on mortality were found; however, statistical models included up to 230 terms, and effects of active smoking on mortality in this cohort were clearly smaller than in other studies, calling into question the modelling approach that was used. Also, data on total mortality only were reported, precluding conclusions with respect to cause-specific deaths. The VA database has been described by the "VA's Seattle Epidemiologic Research and Information Centre" as being less suitable for etiological research of this kind (15). The first European cohort study was reported from the Netherlands (12), suggesting that exposure to traffic-related air pollution including PM was associated with increased cardio-pulmonary mortality in subjects living close to main roads.

The relationship between air pollution and lung cancer has also been addressed in several case-control studies (16, 17). A study from Sweden found a relationship with motor vehicle emissions, estimated as the NO_2 contribution from road traffic, using retrospective dispersion modelling (18, 19). Diesel exhaust may be involved in this (20, 21) but so far, diesel exhaust has not been classified by the International Agency for Research on Cancer (IARC) as a proven human carcinogen. However, new evaluations are underway both in the United States and at the

IARC, as new studies and reviews have appeared since IARC last evaluated diesel exhaust in 1989.

Studies focusing on morbidity endpoints of long-term exposure have been published as well. Notably, work from Southern California has shown that lung function growth in children is reduced in areas with high PM concentrations (22, 23) and that the lung function growth rate changes in step with relocation of children to areas with higher or lower PM concentrations that before (24).

Short-term studies

The database on short-term effects of PM on mortality and morbidity has been augmented by numerous new studies. Two large multi-centre studies from the United States of America (National Morbidity, Mortality, and Air Pollution Study, NMMAPS) and Europe (Air Pollution and Health: a European Approach, APHEA) have produced effect estimates that are more precise than those available six years ago. They are also different in magnitude (generally smaller), so that estimates of health impact based on current exposure-response relationships will be different from estimates based on the relationships published in the previous WHO AQG report. The new studies have also addressed issues such as thresholds and extent of mortality displacement (25, 26, 27, 28, 29, 30). Published effect estimates from APHEA and NMMAPS are presented in Table 1. In spring 2003, St. George's Medical School in London is conducting a systematic meta-analysis including APHEA and NMMAPS. Recently, questions have been raised as to the optimal statistical methodology to analyse time series data (31, 32, 33, 34), and it has been shown that in the NMMAPS data, effect estimates were considerably reduced when alternative models were applied to the data. A peer-reviewed report is being prepared for publication in the spring of 2003 by HEI to discuss to what extent published effect estimates for a series of other studies should change because of this.

It has become clear that not all methodological questions surrounding the modelling of time series data on air pollution and mortality and morbidity will be resolved in the near future. In the interests of public health, the best currently available effect estimates need to be used to update the exposure-response relationships for PM published in the previous WHO AQG. As a result of the meta-analysis of St. George's Medical School in London, and the HEI report mentioned above that will be available before the summer of 2003, revised exposure-response relationships will be adopted. Preliminary results of the meta-analysis of St. George's Medical School suggest that after adjustment for publication bias, 26 studies that have not used the potentially flawed GAM methods result in an estimate of a 0.4% increase in daily mortality per 10 $\mu g/m^3$ PM_{10}, an estimate very close to the uncorrected NMMAPS and APHEA estimates mentioned in table 1 (35).

The mortality and morbidity time series studies have shown, much more clearly than before, that cardiovascular deaths and morbidity indicators are related to ambient PM (36, 37, 38, 39, 40, 41, 42, 43). The quoted references are just a small selection of key papers on the link between PM and cardiovascular endpoints that have appeared in recent years. Understanding of the mechanistic background of relations between ambient PM and cardiovascular endpoints has increased (see below). Compared to when the previous WHO AQG were developed, insights into cardiovascular disease (CVD) effects of ambient PM have increased multifold. The new work on relations between PM and arteriosclerosis provides an interesting background to observed relations between PM and mortality in the cohort studies (41, 43). Possibly, ultrafine particles (smaller than 100 nm) play a role here, as these may be relocated from the respiratory system

into systemic circulation (44, 45) where they may lead to thrombosis (46). The epidemiological database is still small, which is in part related to the technical difficulties in performing exposure assessment for ultrafine particles in the field. Further discussion of the possible role of ultrafines can be found in the rationale for the answer to question 7.

Black smoke

"Black smoke" (BS) refers to a measurement method that uses the light reflectance of particles collected in filters to assess the "blackness" of the collected material. The method was originally developed to measure smoke from coal combustion, and a calibration curve exists, developed in the 1960s, that translates the reflectance units into a mass number. That translation is no longer valid as was shown in a Europe-wide study conducted in the winter of 1993/1994 (47, 48). However, the measurement of light reflectance of PM filters has been shown to be highly correlated with elemental carbon in some recent studies (49, 50). In several recent European studies, BS was found to be at least as predictive of negative health outcomes as PM_{10} or $PM_{2.5}$ (51, 52). The Dutch cohort study reported that traffic-related pollution, as indexed by NO_2 was strongly associated with long-term mortality rates, while Laden et al. (53) indicated, based on source-apportionment, that excess daily mortality was more closely associated with traffic pollution than any other source category analysed. These findings indicate that black smoke, which is closely-related in the modern urban setting with diesel engine exhaust, could serve as a useful marker in epidemiological studies, perhaps even retrospective analyses using the historic data available in many European urban areas.

Since routine monitoring methods for the coarse fraction $PM_{(10–2.5)}$ and ultrafine particle number concentration are not yet established, it is prudent to maintain established PM_{10} monitoring programme for a number of additional years. While estimates of $PM_{(10–2.5)}$ from the algebraic difference of $PM_{2.5}$ and PM_{10} measurements have an unfortunately high degree of imprecision, especially when $PM_{2.5}$ is a major fraction of the PM_{10} concentration, the resulting estimates of $PM_{(10–2.5)}$ can still be informative about the need in future for more direct measurements of the mass concentration of $PM_{(10–2.5)}$. They can also be useful for refinement of new methods that can provide future monitoring data simultaneously on $PM_{2.5}$, $PM_{(10–2.5)}$, and black smoke. The working group recommends that consideration for this option be given to an optimized dichotomous sampler, with photometric analysis of black smoke on the $PM_{2.5}$ filter.

For these reasons, and because BS concentrations are much more directly influenced by local traffic sources, it is recommended to re-evaluate BS as part of the reconsideration of the WHO Air quality guidelines.

Toxicological studies

Concentrations of PM that are somewhat higher than those common in ambient air in cities, are necessary to induce toxic effects in very short-term clinical experimental studies. Exposure to concentrated ambient air particles (23–311 $\mu g/m^3$) for 2 hours induced transient, mild pulmonary inflammatory reactions in healthy human volunteers exposed to the highest concentrations, with an average of 200 $\mu g/m^3$ $PM_{2.5}$ (54). However, no other indicators of pulmonary injury, respiratory symptoms or decrements in pulmonary function were observed in association with exposure. In another study, exposure to ambient air particles (23–124 $\mu g/m^3$) for 2 hours did not induce any observed inflammation in healthy volunteers (55). Although technical difficulties still affect comparison with ambient air conditions, these studies have made it possible to explore possible effects at somewhat higher concentrations leading to a more comprehensive

understanding of the processes involved. The effects measured in healthy individuals in these studies appear to be mild. Also studies with diesel exhaust show mild effects in individuals with compromised health (56). Controlled human exposure studies with diesel engine exhaust showed clear inflammatory effects locally in the respiratory tract, as well as systemically (56, 57, 58, 59, 60, 61, 62).

Animal exposure studies have generally supported many of the findings reported in human studies and have provided additional information about mechanisms of toxicity. However, the limited toxicological data and knowledge of the mechanisms of PM effects and of the characteristics of PM that produce effects constrains the interpretation of these data. Furthermore, there are many unresolved issues when attempting to extrapolate findings in animal studies to humans, including the appropriateness of the various animal models, the particular kinds of particles used, and the health-related endpoints being assessed. A number of in vivo and in vitro studies demonstrate that ambient urban particulates may be more toxic than some surrogate particles such as iron oxide or carbon particles (63, 64). For animal models of chronic bronchitis, cardiac impairment, or lung injury, increased susceptibility to PM has been established (63, 65, 66, 67). Animal studies have also shown that fine particulate matter recovered from cities can cause lung inflammation and injury (63). Changes in cardiac function have also been replicated in animals exposed to PM collected from cities and provide insights on the mechanisms of PM toxicity (68, 69, 70, 71).

Several toxicological studies with different types of particles have been conducted during the last few years, pointing to different particle characteristics as being of importance for toxic effects. Among the parameters that play an important role for eliciting health effects are the size and surface of particles, their number and their composition, e.g. their content of soluble transition metals (72).

2) Which effects can be expected of long-term exposure to levels of PM observed currently in Europe (include both clinical and pre-clinical effects, e.g. development of respiratory system)?

Answer:

Long-term exposure to current ambient PM concentrations may lead to a marked reduction in life expectancy. The reduction in life expectancy is primarily due to increased cardio-pulmonary and lung cancer mortality.

Increases are likely in lower respiratory symptoms and reduced lung function in children, and chronic obstructive pulmonary disease and reduced lung function in adults.

Rationale:
Given the absence of clearly documented thresholds in the exposure-response relationships for long-term as well as short-term effects (see answer and rationale to question 3), and given the fact that these exposure response relationships have been established in studies at currently observed exposure ranges, adverse effects on health occur with certainty in Europe. Such effects are a reduction of life expectancy by up to a few years (73), with possibly some contribution from increased infant mortality in the more highly exposed areas (73, 74, 75), as increased chronic bronchitis and chronic obstructive pulmonary disease (COPD) rates, reduced lung

function and perhaps other chronic effects. Recently it was shown that a part of effects of air pollution on life expectancy can also be calculated using time series studies (76). For almost all types of health effects, data are available not only from studies conducted in the United States of America and Canada (77, 78), but also from Europe (18, 79), which adds strength to the conclusions.

A recent estimate for Austria, France and Switzerland (combined population of about 75 million) is that some 40 000 deaths per year can be attributed to ambient PM (80). Similarly high numbers have been estimated for respiratory and cardiovascular hospital admissions, bronchitis episodes and restricted activity days. The Global Burden of Disease project has recently expanded its analysis of the impact of common risk factors on health to include environmental factors. It has been estimated that exposure to fine particulate matter in outdoor air leads to about 100 000 deaths (and 725 000 years of life lost) annually in Europe (2).

Strong evidence on the effect of long-term exposure to PM on cardiovascular and cardiopulmonary mortality comes from cohort studies (see also rationale to question 1). The ACS study (81) found an association of exposure to sulfate and mortality. In the cities where also $PM_{2.5}$ has been measured, this parameter showed the strongest association with mortality. The re-analysis by HEI (10) essentially found the same results. As described in Pope et al. (13) the ACS cohort was extended, the follow-up time was doubled to 16 years and the number of deaths was tripled. The ambient air pollution data were expanded substantially, data on covariates were incorporated and improved statistical modelling was used. For all causes and cardiopulmonary deaths, statistically significant increased relative risks were found for $PM_{2.5}$. TSP and coarse particles ($PM_{15} - PM_{2.5}$) were not significantly associated with mortality. The US-Harvard Six Cities Study (82) examined various gaseous and PM indices (TSP, $PM_{2.5}$, SO_4^-, H^+, SO_2 and ozone). Sulfate and $PM_{2.5}$ were best associated with cardiopulmonary and cardiovascular mortality. The re-analysis of HEI (10) also essentially confirmed these results.

A random sample of 5000 people was followed in a cohort study from the Netherlands (12). The association between exposure to air pollution and (cause specific) mortality was assessed with adjustment for potential confounders. Cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI 1.09–3.52) and, less consistently, with the estimated ambient background concentration (1.34, 0.68–2.64). The relative risk for living near a major road was 1.41 (0.94–2.12) for total deaths. Non-cardiopulmonary, non-lung cancer deaths were unrelated to air pollution (1.03, 0.54–1.96 for living near a major road). The authors conclude that long-term exposure to traffic-related air pollution may shorten life expectancy.

Of the long-term cohort studies discussed above, the Harvard Six Cities Study found an increased, but statistically non-significant risk for $PM_{2.5}$ and lung cancer (82). The extended ACS study reported a statistically significant association between living in a city with higher $PM_{2.5}$ and increased risk of dying of lung cancer (13). The ASHMOG study found increases in lung cancer incidence and mortality to be most consistently associated with elevated long-term ambient concentrations of PM_{10} and SO_2, especially among males (9).

A few animal studies using long-term exposure to diluted diesel motor exhaust (DME) have been reported. There is extensive evidence for the induction of lung cancer in rats, but not in hamsters or mice, from chronic inhalation of high concentrations of diesel soot. High particle deposition-related inflammatory effects, including generation of high concentration of oxygen radicals and increased oxidative DNA damage in proliferating epithelial lung cells, may be the mechanism by which particles induce lung tumours in rats (83, 84). However, there may be a threshold for this

effect, well above environmental exposure levels (85, 86). No inflammatory or other toxic effects were found in rats chronically exposed to lower concentrations of DME (87). The exposure of young adult humans for 2 hours to diesel engine exhaust in the same lower concentration range as in the rat study (87) caused clear inflammatory effects in the lung (56, 57, 58, 59, 60, 61, 62). Thus, this kind of particle-induced inflammation, together with the carcinogenic potential of diesel soot-attached PAH, may add to the air pollutant-related lung cancer in humans. Diesel particulate matter is formed not only by the carbon nucleus but also a wide range of different components, and its precise role in diesel exhaust-induced carcinogenicity is unclear. However, in high-exposure animal test systems, diesel particulate matter has been shown to be the most important fraction of diesel exhaust (84).

In the Harvard 24 Cities study, significant associations of lung function parameters (FEV1, FVC) and increase of bronchitis with acidic particles (H^+) were found (77, 78) for American and Canadian children. McConnell et al. (88) noted in a cohort study from California that as PM_{10} increased across communities, an increase in bronchitis also occurred. However, the high correlation of PM_{10}, acid, and NO_2 precludes clear attribution of the results of this study specifically to PM alone. In Europe, Heinrich et al. (89, 90, 91) performed three consecutive surveys on children from former East Germany. The prevalence of bronchitis, sinusitis and frequent colds was 2–3 fold increased for a 50 µg/m^3 increment in TSP. Krämer et al. (92) investigated children in six communities in East and West Germany repeatedly over 6 years. A decrease of bronchitis was seen between beginning and end of the study, being most strongly associated with TSP. Braun-Fahrländer et al. (79) investigated the effect of long-term exposure to air pollution in a cross-sectional study on children from 10 Swiss communities. Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. Collinearity of PM_{10}, NO_2, SO_2 and O_3 prevented any causal separation of pollutants. Ackermann-Liebrich et al. (93) and Zemp et al. (94) performed a similar study on adults from eight Swiss communities. They found that chronic cough and chronic phlegm and breathlessness were associated with TPS, PM_{10} and NO_2, and that lung function (FEV1, FVC) was significantly reduced for elevated concentrations of PM_{10}, NO_2 and SO_2.

Jedrychowski et al. (95) reported an association between both BS and SO_2 levels in various areas of Krakow, Poland, and slowed lung function growth (FVC and FEV1). In the Children's Health Study in Southern California, the effects of reductions and increases in ambient air pollution concentrations on longitudinal lung function growth have been investigated (24). Follow-up lung function tests were administered to children who had moved away from the study area. Moving to a community with lower ambient PM_{10} concentration was associated with increasing lung function growth rates, and moving to a community with higher PM_{10} concentrations was associated with decreased growth.

In addition to aggravation of existing allergy, particulates have been shown in some experimental systems to facilitate or catalyse an induction of an allergic immune response to common allergens (96). However, epidemiological evidence for the importance of ambient PM in the sensitization stage is scarce.

3) Is there a threshold below which no effects on health of PM are expected to occur in all people?

Answer:

Epidemiological studies on large populations have been unable to identify a threshold concentration below which ambient PM has no effect on health. It is likely that within any large human population, there is such a wide range in susceptibility that some subjects are at risk even at the lowest end of the concentration range.

Rationale:

The results from short-term epidemiological studies suggest that linear models without a threshold may well be appropriate for estimating the effects of PM_{10} on the types of mortality and morbidity of main interest. This issue has been formally addressed in a number of recent papers (26, 97, 98). Methodological problems such as measurement errors (99, 100) make it difficult to precisely pinpoint a threshold if it exists; effects on mortality and morbidity have been observed in many studies conducted at exposure levels of current interest. If there is a threshold, it is within the lower band of currently observed PM concentrations in Europe. As PM concentrations are unlikely to be dramatically reduced in the next decade, the issue of the existence of a threshold is currently of more theoretical than practical relevance.

At high concentrations as they may occur in episodes or in more highly polluted areas around the world, linearity of the exposure response relationship may no longer hold. Studies (98, 101) suggest that the slope may become more shallow at higher concentrations, so that assuming linearity will over-estimate short-term effects at high concentration levels.

The results from studies of long-term exposures also suggest that an exposure-response relationship down to the lowest observed levels seems to be appropriate. Graphs presented in the recently published further follow-up of the ACS cohort (13) suggest that for cardiopulmonary mortality, and especially for lung cancer mortality, the risk was elevated even at (long-term) $PM_{2.5}$ levels below 10 $\mu g/m^3$. The graphs presented in the ACS cohort paper suggest that at the lowest concentrations, the exposure-response relationships for lung cancer and cardiopulmonary deaths were even somewhat steeper than at higher concentrations, but uncertainties in the exposure-response data preclude firm conclusions as to non-linearities of the relationships.

In the lung, different defence mechanisms exist that can deal with particles. Particles may be removed without causing damage, potentially damaging particle components may be neutralized, reactive intermediates generated by particles may be inactivated or damage elicited by particles may be repaired. Based on a mechanistic understanding of non-genotoxic health effects induced by particles, the existence of a threshold because of these defence mechanisms is biologically plausible. However, the effectiveness of defence mechanisms in different individuals may vary and therefore a threshold for adverse effects may be very low at the population level in sensitive subgroups. A range of thresholds may exist depending on the type of effect and the susceptibility of individuals and specific population groups. Individuals may have thresholds for specific responses, but they may vary markedly within and between populations due to inter-individual differences in sensitivity. At present it is not clear which susceptibility characteristics from a toxicological point of view are the most important although it has been shown that there are large differences in antioxidant defences in lung lining fluid between healthy subjects (102, 103, 104). The toxicological data on diesel exhaust particles in healthy animals may indicate a threshold of

response (86, 87), whereas the data on compromised animals are too scarce to address this issue properly.

4) Are effects of the pollutant dependent upon the subjects' characteristics such as age, gender, underlying disease, smoking status, atopy, education etc? What are the critical characteristics?

Answer:

In short-term studies, elderly subjects, and subjects with pre-existing heart and lung disease were found to be more susceptible to effects of ambient PM on mortality and morbidity. In panel studies, asthmatics have also been shown to respond to ambient PM with more symptoms, larger lung function changes and with increased medication use than non-asthmatics.
In long-term studies, it has been suggested that socially disadvantaged and poorly educated populations respond more strongly in terms of mortality. PM also is related to reduced lung growth in children.
No consistent differences have been found between men and women, and between smokers and non-smokers in PM responses in the cohort studies.

Rationale:
The very young and the very old, as well as persons with lower socio-economic status are apparently especially affected by PM air pollution. In the time series studies, it has been well established that elderly subjects (and possibly, very young children) are more at risk than the remainder of the population (105). Subjects with pre-existing cardiovascular and respiratory disease are also at higher risk (38, 106). This is similar to the experiences of the populations exposed to the London 1952 smog episode, despite the fact that exposures were in the mg/m^3 rather than in the $\mu g/m^3$ range then. Children with asthma and bronchial hyper-responsiveness have also been shown to be more susceptible to ambient PM (107, 108) although effects have been observed in non-symptomatic children as well. In addition, low socio-economic status seems to convey higher risks for morbidity associated with PM in short term studies (109). With exercise, deposition patterns of particles change, and it has been shown that the fractional deposition of ultrafine particles is particularly increased with exercise (110). In the cohort studies from the United States of America there was no difference in air pollution risks between smokers and non-smokers.

In the HEI re-analysis project, the subjects' characteristics were addressed in detail as determinants of PM-mortality associations. An intriguing finding was that effects of PM on mortality seemed to be restricted largely to subjects with low educational status (10). This finding was repeated in the Dutch cohort study (12) and in the further ACS follow-up (13). In the AHSMOG study, subjects classified as having low antioxidant vitamin intake at baseline were found to be at higher risk of death due to PM air pollution than subjects with adequate intakes (9, 111). It seems that attributes of poor education (possibly nutritional status, increased exposure, lack of access to good-quality medical care and other factors) may modify the response to PM.

Controlled human exposure studies and studies on animals with age-related differences or certain types of compromised health, have also shown differences in susceptibility to PM exposure (56, 66, 70, 112, 113, 114). Results suggest that effects of particles on allergic immune responses may differ between healthy and diseased individuals, but the relative importance of genetic

background and pre-existing disease is not clear. Age-related differences in rodents exhibit differences in susceptibility that do not provide a clear picture at present. Molecular studies of humans, animals and cells indicate the importance of a number of susceptibility genes and their products. For lung cancer certain growth-, cell death-, metabolism- and repair-controlling proteins may in part explain differences in susceptibility (115). For other lung diseases related to radical production and inflammation, proteins such as surfactant proteins and Clara cell protein (116) may play an important role and thus contribute to differences in susceptibility.

Some studies using high exposures to PM indicate that animals with pre-existing cardiovascular disease are at greater risk for exacerbation of their disease than their healthy counterparts (44, 70, 112).

Although factors such as lifestyle, age and pre-existing disease seem to be emerging as susceptibility parameters, and certain gene products may partly explain individual variation in susceptibility, the issue of inter-individual susceptibility to PM still needs further research adequately to describe susceptibility characteristics. Adequate animal models have been difficult to develop, and there are still difficulties in extrapolating results from animal studies to the human situation.

5) To what extent is mortality being accelerated by long and short-term exposure to the pollutant (harvesting)?

Answer:

Cohort studies have suggested that life expectancy is decreased by long-term exposure to PM. This is supported by new analyses of time-series studies that have shown death being advanced by periods of at least a few months, for causes of death such as cardiovascular and chronic pulmonary disease.

Rationale:

Several recent papers have addressed the issue of "mortality displacement (harvesting)" in the context of time-series studies (8, 25, 28, 30); the methodological limitation of these analyses is that they cannot move beyond time scales of a few months (because at longer time scales, seasonal variation in mortality and morbidity becomes hard to control for). Nevertheless, these analyses have shown that the mortality displacement associated with short-term PM exposures does not take place on a timeframe of only a few days. One analysis suggested that mortality displacement was limited to a few months for deaths due to obstructive pulmonary disease, but that effects were increasing with increasing PM averaging time for deaths due to pneumonia, heart attacks and all-cause mortality (28), suggesting that cumulative exposures are more harmful than the short-term variations in PM concentrations. These findings imply that effect estimates as published from the NMMAPS and APHEA studies (see Table 1) which are based on single-day exposure metrics, are likely to *under*estimate the true extent of the pollution effects.

The cohort study findings are more suitable for calculations of effects on life expectancy. Several authors (8, 73, 117, 118, 119) have concluded that at current ambient PM levels in Europe, the effect of PM on life expectancy may be in the order of one to two years. Several studies have shown effects of long-term PM exposure on lung function (22, 23, 78, 93), and as reduced lung function has been shown to be an independent predictor of mortality in cohort studies (120, 121),

the effects of PM on lung function may be among the causal pathways through which PM reduces life expectancy.

A particularly difficult issue to resolve is to what extent exposures early in life (which were presumably much higher than recent exposures in many areas) contribute to mortality differences as seen today in the cohort studies. In the absence of historical measurement data, and of life-long mortality follow-up in the cohort studies, this question cannot be answered directly. The health benefits of smoking cessation have been well investigated and offer some parallel to PM in ambient air. Studies show that cardiovascular disease risk is reduced significantly soon after smoking cessation, and that even the lung cancer risk in ex-smokers who stopped smoking 20 or more years ago, is nearly reduced to baseline (122, 123, 124). This suggests that exposures to inhaled toxicants in the distant past may not lead to large differences in mortality between populations studied long after such high exposures have ceased.

Toxicological studies as currently being conducted are unable to address the issue of "mortality displacement" by ambient PM.

6) Is the considered pollutant per se responsible for effects on health?

Answer:

Ambient PM per se is considered responsible for the health effects seen in the large multi-city epidemiological studies relating ambient PM to mortality and morbidity such as NMMAPS and APHEA. In the Six Cities and ACS cohort studies, PM but not gaseous pollutants with the exception of sulfur dioxide was associated with mortality. That ambient PM is responsible per se for effects on health is substantiated by controlled human exposure studies, and to some extent by experimental findings in animals.

Rationale:

To what extent PM as such is responsible for effects on health is a very important question. The sometimes high correlation between PM and some gaseous components of ambient air pollution makes it difficult to statistically separate their effects on health. The one exception is ozone: in many areas and time series, the correlation between PM and ozone is weak or sometimes even negative. Mutual adjustment has been shown even to increase effects of PM as well as ozone in some areas (51). PM effects seen in epidemiological studies do not reflect ozone effects, nor vice versa. .

The multi-city time series study NMMAPS has found PM effects to be insensitive to adjustment for a number of gaseous pollutants. In the APHEA study and in a Canadian study conducted in eight cities, adjustment for NO_2 reduced PM effect estimates by about half (29, 125); ambient NO_2 is likely to act as a surrogate for traffic-related air pollution including very small combustion particles in these studies; nevertheless, these findings show that measurement of PM_{10} or $PM_{2.5}$ alone is not sufficient to represent fully the impact of complex air pollution mixtures on mortality (see also NO_2 document). Several authors have shown rather convincingly that SO_2 is not a likely confounder of associations between PM and health in short-term studies also by pointing to large changes in SO_2 effect estimates after large reductions in SO_2 concentrations over time (126, 127). Such changes in effect estimates show that SO_2 per se is not responsible, but co-varies with other components that are.

The issue is more complicated for the long-term studies, as the HEI re-analysis project has flagged SO_2 as an important determinant of mortality in the ACS cohort study. To what extent SO_2 is a surrogate for small-area spatial variations of air pollution components (including PM) not captured by single city background monitoring sites remains unclear in the ACS study. The Dutch cohort study focused primarily on such small-area variations in traffic-related air pollution, and was conducted at a time when SO_2 concentrations were already low, so confounding by SO_2 may not have been an issue there. NO_2 co-varies with PM in all areas where traffic is a major source of PM. It then becomes hard to separate these two using statistical tools. It should be noted that when areas with high and low traffic contributions to ambient PM are included in time series studies (as in APHEA), the correlation between ambient PM and NO_2 becomes less, and the two can be analysed jointly. In addition, important insights have been provided in a study on predictors of personal exposure to PM and gaseous components conducted among non-smokers living in non-smoking households (128). It was shown that ambient PM predicted personal PM concentrations well on a group level however, ambient gaseous air pollution concentrations were not correlated with personal gaseous air pollution concentrations, which were also found to be much lower than ambient concentrations, presumably due to incomplete penetration of gases to indoor spaces, and reactions of gases with indoor surfaces. Interestingly, ambient ozone concentrations predicted personal $PM_{2.5}$ (positive in summer, negative in winter), ambient NO_2 predicted personal $PM_{2.5}$ in winter as well as summer, ambient CO predicted personal $PM_{2.5}$ in winter, and ambient SO_2 was negatively associated with personal $PM_{2.5}$. These results suggest that ambient gaseous pollution concentrations are better surrogates for personal PM of outdoor origin than for personal exposure to the gaseous components themselves.

Although these arguments support an independent role of PM, they do not distinguish PM components from each other in relation to toxicity. Indeed, it has been very difficult to show convincingly that certain PM attributes (other than size) are more important determinants of ill health than others. This issue is treated more completely in the answer to the 7th question.

The controlled human exposure data show a direct effect of PM on the induction of inflammation in humans at concentrations that are somewhat higher than generally encountered in ambient air (see question 1). Thus, the data in part substantiate the findings in epidemiological studies that PM as such, is a major contributor to health effects. Studies with experimental animals also to some extent support the epidemiological data (113, 129). A recent paper has shown that especially coarse-mode PM contains relatively high levels of bacterial endotoxin, and that the biological activity of these particles is clearly related to the endotoxin level (130). This is an interesting observation that may account for findings in epidemiological studies showing associations between coarse PM exposure and health effects.

The plausibility of associations between PM and health continues to be discussed. Gamble and Nicolich have argued that the PM doses required to elicit adverse effects in humans by active smoking and various occupational exposures are orders of magnitude higher than doses obtained from ambient PM exposures (131). However, when ambient PM exposures are compared to environmental tobacco smoke (ETS) exposure, the doses are of comparable magnitude, and IARC has recently decided that ETS should be classified as a proven human carcinogen (132).

7) For PM: which of the physical and chemical characteristics of particulate air pollution are responsible for health effects?

Answer:

There is strong evidence to conclude that fine particles (< 2.5 μm, $PM_{2.5}$) are more hazardous than larger ones (coarse particles) in terms of mortality and cardiovascular and respiratory endpoints in panel studies. This does not imply that the coarse fraction of PM_{10} is innocuous. In toxicological and controlled human exposure studies, several physical, biological and chemical characteristics of particles have been found to elicit cardiopulmonary responses. Amongst the characteristics found to be contributing to toxicity in epidemiological and controlled exposure studies are metal content, presence of PAHs, other organic components, endotoxin and both small (< 2.5 μm) and extremely small size (< 100 nm).

Rationale:

Possibly relevant physical characteristics of PM are particle size, surface and number (which are all related). The smaller the particle, the larger is the surface area available for interaction with the respiratory tract, and for adsorption of biologically active substances.

Epidemiology

Quite a few studies suggest that fine PM is more biologically active than coarse PM (defined as particles between 2.5 and 10 μm in size) (14, 133, 134, 135)) but other studies have also found that coarse PM is associated with adverse health effects (136, 137, 138, 139, 140); the relative importance of fine and coarse PM may depend on specific sources present in some areas but not others. A more extensive discussion of the new literature on $PM_{2.5}$ can be found in the rationale for the answer given to question 1.

The number of ultrafine (< 100 nm) particles in air has been subject to research in recent years, following suggestions (113, 141, 142) that such particles may in particular be involved in the cardiovascular effects often seen to be associated with PM. In addition, vehicular traffic has been shown to be an important source of ultrafine particles, and very high number concentrations have been observed near busy roads, with steep gradients in concentration at distances increasing up to several hundred metres from such roads (143, 144, 145). Insights gained have been that in most situations, the (time series) correlation between PM mass and ultrafine particles is low (146); as a result, associations between PM mass and health endpoints and mortality and morbidity seen in time series studies cannot readily be explained by the action of ultrafine particles. A small number of studies have been conducted on ultrafine particles, some of which suggest associations with mortality and with asthma exacerbations (127, 147, 148, 149, 150). It should be noted that ultrafine particles are inherently unstable in the atmosphere because they coagulate quickly. Exposure assessment based on single ambient monitoring stations is therefore more subject to error than for PM mass. More research is needed to establish the possible links between ultrafine PM sources, exposures and health more accurately and precisely.

Possibly relevant chemical characteristics include the content of transition metals, crustal material, secondary components such as sulphates and nitrates, polycyclic aromatic hydrocarbons and carbonaceous material, reflecting the various sources that contribute to PM in the atmosphere. In general, fine PM (< 2.5 μm) consists to a large extent of primary and secondary combustion products such as elemental and organic carbon, sulphates, nitrates and PAHs. Coarse PM (between 2.5 and 10 μm) usually contains more crustal material such as silicates. So far, no single component has been identified that could explain most of the PM effects. Studies from Utah Valley have suggested that close to steel mills, transition metals could be important (151, 152, 153, 154); in urban situations with lower transition metal concentrations,

this has not yet been clearly established. Few large-scale epidemiological studies have addressed the role of specific particle metals; work from Canada suggested that iron, zinc and nickel may be especially important (125).

Other studies, using source apportionment techniques, have pointed to traffic and coal combustion as important sources of biologically active PM (53, 155). In many time series and in some of the cohort and cross sectional studies, sulphates are found to predict adverse effects well (13, 51, 77, 135, 138, 156, 157, 158, 159, 160). It has been suggested that this may be related to interactions between sulphate and iron in particles (161) but it should be pointed out that in animal experiments, it has generally not been possible to find deleterious effects of sulphate aerosols even at concentrations much higher than ambient (162, 163).

Toxicology
Many toxicological studies, both in vivo and in vitro and in human as well as in animal systems, have attempted to determine the most important characteristics of PM for inducing adverse health effects. Some studies have demonstrated the importance of particle size (ultrafine vs. fine vs. coarse particles), surface area, geometric form, and other physical characteristics. Others have focused on the importance of the non-soluble versus soluble components (metals, organic compounds, endotoxins, sulphate and nitrate residues). The relative potency of the different characteristics will differ for the various biological endpoints, such as cardiovascular effects, respiratory inflammation/allergy and lung cancer. The importance of the different determinants will vary in urban settings with different PM profiles. Thus, it is likely that several characteristics of PM are crucial for the PM-induced health effects and none of the characteristics may be solely responsible for producing effects.

Particle size: Studies with experimental animals have shown that both the coarse, fine and ultrafine fractions of ambient PM induce health effects (113, 129, 164). On a mass basis, small particles generally induce more inflammation than larger particles, due to a relative larger surface area (165). The coarse fraction of ambient PM may, however, be more potent to induce inflammation than smaller particles due to differences in chemical composition (129). Experimentally, inhaled ultrafine particles have been demonstrated to pass into the blood circulation and to affect the thrombosis process (45, 46). The molecular and pathophysiological mechanisms for any PM-induced cardiovascular effects are largely unknown.

Metals: There is increasing evidence that soluble metals may be an important cause of the toxicity of ambient PM. This has been shown for the ambient air in Utah Valley, where a steel mill is a dominant source (72, 166, 167). Furthermore, water-soluble metals leached from residual oil fly ash particles (ROFA) have consistently been shown to contribute to cell injury and inflammatory changes in the lung (65, 154). The transition metals are also important components concerning PM-induced cardiovascular effects (65). Transition metals potentiate the inflammatory effect of ultrafine particles (168). However, it has not been established that the small metal quantities associated with ambient PM in most environments are sufficient to cause health effects. Metals considered to be relevant are iron, vanadium, nickel, zinc and copper (8). In a comparative study of pulmonary toxicity of the soluble metals found in urban particulate dust from Ottawa, it has recently been reported that zinc, and to a lesser degree copper, induced lung injury and inflammation, whereas the responses to the nickel, iron, lead and vanadium were minimal (169).

Organic compounds: Organic compounds are common constituents of combustion-generated particles, and comprise a substantial portion of ambient PM. A number of organic compounds

extractable from PM (especially PAHs) should be considered to exert pro-inflammatory as well an adjuvant effects (170, 171). Some of the PAHs and their nitro-and oxy-derivatives have been shown to be mutagenic in bacterial and mammalian systems and carcinogenic in animal studies, but most of the organic compounds responsible for the majority of the mutagenicity of ambient air have not been identified (3, 8).

Endotoxins: The bacterial endotoxins (lipopolysaccharides), known to exert inflammatory effects, are virtually ubiquitous and have been shown to be present in both indoor and outdoor PM, but mainly in the coarse (PM_{10}) fraction (172). The endotoxins may contribute to the health effects of urban air particulates, although this has not been shown at lower concentrations. As mentioned before, recent evidence has implicated endotoxin especially in the biological activity of coarse PM (130).

Acidic aerosols: Acidic aerosols have been shown to elicit increased airway responsiveness in asthmatics. These effects are, however, only seen with highly acidic particles (sulphuric acid aerosols) at concentrations many times above ambient levels (173).

8) What is the evidence of synergy / interaction of the pollutant with other air pollutants?

Answer:

Few epidemiological studies have addressed interactions of PM with other pollutants. Toxicological and controlled human exposure studies have shown additive and in some cases, more than additive effects, especially for combinations of PM and ozone, and of PM (especially diesel particles) and allergens. Finally, studies of atmospheric chemistry demonstrate that PM interacts with gases to alter its composition and hence its toxicity.

Rationale:

Synergistic and antagonistic interactions are difficult to estimate in epidemiological studies, because they usually require large sample sizes to establish them with sufficient confidence. Perhaps the best example to quote here is APHEA2 that found that PM effects on mortality were stronger in areas with high NO_2 (29). But even this finding, although formally pointing to positive interaction, has been interpreted more as showing that in areas with high NO_2, PM likely contains more noxious substances than in areas with low NO_2.

The evidence of potentiation/synergy (more than additive) is clearer from experimental studies, especially for interactions between PM and ozone. Ozone has been found to increase lung permeability in both animals and human, as well as to increase bronchial hyper-responsiveness. It is therefore expected that combined exposure to ozone and PM would have a more than additive effect. Results from several animal studies with PM show an increase in response with co-exposure to ozone (141, 174, 175). From the single controlled human exposure study available, it was found that combined exposure to a mixture of concentrated ambient particles and ozone may produce vasoconstriction (176). However, no pulmonary endpoints were examined, and the effects of PM and ozone were not evaluated separately. Therefore, the study gives little information on potentiation/synergy between PM and ozone. There are few studies concerning any interaction of PM with single pollutants other than ozone. Interactions of particles and allergens have been studied in controlled human exposure studies and animal

experiments. In animals, adjuvant effects of particles including diesel exhaust particles, have been demonstrated (96, 177). Furthermore, adjuvant effects have also been observed in humans using diesel exhaust particles (178). It is also possible that some interactions could be adaptive. For example, chronic exposure to SO_2 causes mucus hyper-secretion and airway narrowing. This would provide a thicker protective mucus barrier and potentially make it more likely that co-exposure to particles would involve more central deposition and more rapid clearance. Similarly, pre-exposure to ozone could up-regulate antioxidant enzymes and thus partially protect against oxidative injury elicited by PM. In principle, answering the present question is possible with animal studies, but too few investigations utilising mixtures have been carried out (179).

9) What is the relationship between ambient levels and personal exposure to the pollutant over short-term and long-term (including exposures indoors)? Can the differences influence the results of studies?

Answer:

Whereas personal exposure to PM and its components is influenced by indoor sources (such as smoking) in addition to outdoor sources, there is a clear relationship on population level between ambient PM and personal PM of ambient origin over time, especially for fine combustion particles. On a population level, personal PM of ambient origin "tracks" ambient PM over time, thus measurements of PM in ambient air can serve as a reasonable "proxy" for personal exposure in time-series studies.

The relationship between long-term average ambient PM concentrations and long-term average personal PM exposure has been studied less. Contributions to personal PM exposure from smoking and occupation need to be taken into account. However, the available data suggest that imperfect relations between ambient and personal PM do not invalidate the results of the long-term studies.

Rationale:

In short-term studies, the relationship between ambient concentrations and personal PM exposures has been studied repeatedly. The relationship between ambient and personal PM varies from person to person, depending on factors such as exposure to environmental tobacco smoke. On a population average, however, the correlation between ambient and personal PM over time is fairly high, supporting the use of ambient PM measurements in time series studies as exposure surrogate (49, 128, 180, 181, 182, 183, 184, 185). Also, the correlations improve when instead of PM_{10}, ambient and personal $PM_{2.5}$, or "black smoke", or sulphates are being correlated. This reinforces the view that variations over time in ambient fine PM are predicting variations over time in personal fine PM as well, as sulphur dioxide and "black smoke" have little or no indoor sources.

This is not to imply that the correlations between ambient PM and personal PM are universally strong. A recent study of non-smoking healthy adults (age 24 to 64) conducted in the Minneapolis-St. Paul metropolitan area found low, non-significant time series correlations between ambient $PM_{2.5}$ and personal $PM_{2.5}$ (186). In this study, the variation in outdoor $PM_{2.5}$ was low which may have contributed to the low correlations. Also, personal $PM_{2.5}$ concentrations were much higher than both home indoor (factor of 2) and outdoor $PM_{2.5}$ concentrations (factor of 2.5) which is in marked contrast to studies among, e.g., elderly subjects

which have found personal, indoor and outdoor $PM_{2.5}$ concentrations to be similar (49). One interesting implication of these findings, if replicated in areas with higher outdoor $PM_{2.5}$ variability, would be that the lack of relations between ambient PM and health endpoints in younger adults that is sometimes seen may reflect a poor exposure estimate rather than lower susceptibility.

Similar analyses have recently been made of the associations between ambient and personal levels of $PM_{2.5}$ and the gaseous components O_3, NO_2, CO and SO_2 (128). It was shown that ambient PM predicted personal PM concentrations well; however, ambient gaseous air pollution concentrations did not predict personal gaseous air pollution concentrations. Interestingly, ambient ozone concentrations predicted personal $PM_{2.5}$ (positive in summer, negative in winter), ambient NO_2 predicted personal $PM_{2.5}$ in winter as well as summer, ambient CO predicted personal $PM_{2.5}$ in winter, and ambient SO_2 was negatively associated with personal $PM_{2.5}$. These results suggest that ambient gaseous pollution concentrations are better surrogates for personal PM of outdoor origin than for personal exposure to the gaseous components themselves. One would expect, therefore, that ambient PM would dominate ambient gases in epidemiological time series associations between air pollution and health; this, however, is not always so, suggesting that ambient PM measurements do not fully capture the toxic potential of complex ambient air pollution mixtures.

Few studies have addressed whether ambient long-term PM concentrations predict long-term personal PM well. This is due partly to the logistical complications involved in measuring personal PM over long periods of time. Analyses conducted within the EXPOLIS study have suggested that long-term ambient PM concentrations predict the population average of a series of personal $PM_{2.5}$ measurements well (187). Early work from the Six Cities Study has shown that personal sulphate measurements conducted in Watertown (low ambient sulphate) were much lower than personal sulphate measurements conducted in Steubenville (high ambient sulphate) which supports the use of outdoor measurements as exposure metric in this long-term study (188).

There are no data from toxicological studies that contribute to answering this question.

10) Which are the critical sources of the pollutant (or, for PM, its components) responsible for health effects?

Answer:

Short-term epidemiological studies suggest that a number of source types are associated with health effects, especially motor vehicle emissions, and also coal combustion. These sources produce primary as well as secondary particles, both of which have been associated with adverse health effects. One European cohort study focused on traffic-related air pollution specifically, and suggested the importance of this source of PM. Toxicological studies have shown that particles originating from internal combustion engines, coal burning, residual oil combustion and wood burning have strong inflammatory potential. In comparison, wind-blown dust of crustal origin seems a less critical source.

Rationale:
Some of the short-term studies suggest that a number of source-types are associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative

burning. Although some unresolved issues remain, the source-oriented evaluation approach, using factor analysis, seems to implicate so far that fine particles of anthropogenic origin, and especially motor vehicle emissions and fossil fuel combustion, are most important (versus crustal particles of geologic origin) in contributing to observed increased mortality risks (53). Other studies have also implicated traffic as one important source of PM related to morbidity and mortality in time series studies (155, 189, 190). The few long-term studies that have been conducted have generally not been analysed to answer the question on the relative importance of sources. The Dutch cohort study, focusing on traffic-related air pollution, has suggested that traffic is an important source of air pollution leading to premature mortality (12). Studies on genotoxicity of traffic fumes conducted in humans have produced mixed results (191, 192, 193); several studies among occupational groups exposed to traffic fumes have documented adverse effects including lung cancer and lung function changes (194, 195, 196, 197). Childhood cancers were not found to be related to traffic-related air pollution in two large studies from Copenhagen (198) and California (199).

Few studies have tried to establish the *temporal* variation in the contribution of specific sources to ambient PM. A study from California has suggested that on high pollution days, the contribution of mobile sources to ambient PM is disproportionately large (200).

Different kinds of combustion particles from power plants and residential heating (residual oil fly ash, coal fly ash, wood heating particles and transport/traffic-related particles) have been found to induce inflammatory/toxic responses after exposure of animals and humans both in vivo and in vitro. In addition, particles released to air from different kinds of factories have been found to have a high inflammatory/toxic potency (72, 153, 154). Windblown sand and soil erosion particles may also contribute to adverse health effects in areas such as southern Europe, but the toxicological effects of such particles have not been characterized systematically. Some of these particles may consist of quartz, known as a very potent inducer of pulmonary fibrosis. However, the potency of quartz varies between different types (201).

In some locations, a dominating source has been identified, such as in Utah Valley. In most instances, such as in urban areas, multiple sources contribute. At present, it is too early to determine the relative potency and contribution of particles from different sources in urban areas with respect to particle-induced toxic effects. The existing studies point to vehicle emissions (diesel exhaust particles) and residential heating/power plant/factory emissions (residual fly ash particles) as being important. Particles abraded from asphalt-paved roads by the use of studded tyres, have been documented to induce cytokine release in vitro and inflammatory reactions in vivo (202). The relative contribution of the different sources will, however, vary in different parts of Europe, between different cities, and between urban and rural areas. Further studies are required to address the present question.

11) Have positive impacts on public health of reductions of emissions and/or ambient concentrations of the pollutant been shown?

Answer:

Positive impacts of reductions in ambient PM concentrations on public health have been shown in the past, after the introduction of clean air legislation. Such positive impacts have also been reported more recently in a limited number of studies. Toxicological findings also suggest that

qualitative changes in PM composition could be of importance for the reduction of PM-induced adverse health effects.

Rationale:

Some studies have addressed directly the question whether public health benefits can be shown as a result of planned or unplanned downward changes in air pollution concentrations. A recent study from Dublin has documented health benefits of the ban on the use of coal for domestic heating enforced in 1990 (203). In the Utah Valley, PM air pollution concentrations decreased strongly during a 14-month strike in a local steel factory in the 1980s, and mortality as well as respiratory morbidity was found to be reduced during this period (204, 205). Studies from the former German Democratic Republic have documented a reduction in childhood bronchitis and improved lung function along with sharp reductions in SO_2 and PM concentrations after the German reunification (90, 91, 92, 206).

On balance, these studies suggest that reduction in ambient PM concentrations brings about benefits to public health. However, available epidemiological intervention studies do not give direct, quantitative evidence as to the relative health benefits that would result from selective reduction of specific PM size fractions. Also, these studies do not yet provide firm grounds for quantitative prediction of the relative health benefits of single-pollutant reduction strategies vs. multi-pollutant reduction strategies. In the discussed "natural experiments", potentially confounding factors other than ambient PM concentrations also may have changed and thus may have modified the size of the changes in health effects.

In the Children's Health Study in Southern California, the effects of reductions and increases in ambient air pollution concentrations on longitudinal lung function growth have been investigated (24). Follow-up lung function tests were administered to children who had moved away from the study area after the baseline lung function test, which was administered while the children lived within the area. Moving to a community with lower ambient PM_{10} concentration was associated with increasing lung function growth rates, and moving to a community with higher PM_{10} concentrations was associated with decreased growth. Corresponding associations with community levels of NO_2 and O_3 were weaker. This study suggests that reduction in long-term ambient PM_{10} levels is indeed associated with improvement of children's lung growth, and that increase in these levels is associated with retardation of lung growth.

A reduction in adverse particle-induced health effects could be expected following a decrease in ambient PM concentrations and/or by qualitative changes in the PM types and their physical properties and chemical composition. The magnitude of a possible favourable effect for public health will depend on the concentrations of the ambient PM in relation to the shape of the dose-response curve for the adverse effects, such as the existence of threshold concentrations and/or a levelling off of the adverse effects at high exposure concentrations. Exposure studies with sensitive human individuals at a relevant concentration range for ambient PM are rare, and exposure periods are usually very short e.g., from Swedish tunnel experiments (207).

Toxicological studies have been performed to examine whether a change in the concentration of inert vs. active components in the PM fraction could reduce the inflammatory/toxic potential of ambient PM. Both controlled human exposures (154, 208) and animal studies (153) using Utah Valley PM_{10} sampled before, during and after closing of the steel factory, showed considerable coherence of inflammatory outcomes in the lung and changes in airway hyper-responsiveness compared to the epidemiological findings. The change of toxicity potential was attributed to a change in metal concentrations in the PM (167). However, to establish the causal relationship

between qualitative changes in ambient PM and time-dependent reduction in toxic/inflammatory potential, further studies are required in other settings with different PM profiles.

12) What averaging period (time pattern) is most relevant from the point of view of protecting human health?

Answer:

As effects have been observed from both short-term and long-term ambient PM exposures, short-term (24 hours) as well as long-term (annual average) guidelines are recommended.

Rationale:
A large number of studies have linked PM concentrations averaged over one to a few days to health endpoints such as daily mortality and hospital admissions. A 24-hour guideline value should be developed because using a one-day averaging time allows transparent linking of the chosen value to the exposure-response relationships that can be derived from the time-series studies. With the advent of instruments that measure ambient PM with high time resolution, studies are now being published which suggest that short-term peak exposures may also be important for events such as triggering myocardial infarctions and attacks of asthma (39, 209). However, the data are yet insufficient to recommend development of guideline values for averaging times of less than 24 hours.

There is now also a substantial body of evidence linking long-term average ambient PM to health effects. Therefore, it is also recommended to develop guideline values for long-term average concentrations of ambient PM. In practice, an annual average will be sufficient to fulfil this need.

When ambient PM is primarily of secondary origin, concentrations tend to be similar over large regions, and annual average concentrations are highly correlated with 24-hour means. On the basis of such relations, a ratio of annual average and expected maximum 24-hour average concentrations can be estimated which may be region specific. On the basis of such ratios, an evaluation is possible of which guideline value (short term or long term) will be the more stringent in a specific area. It is recommended that guideline values be developed for long term and short term averaging times independently, on the basis of the exposure-response relationships, as they exist for long-term and short-term exposures. The evaluation of expected ratios can then be used as a tool for policy makers to decide whether they should focus primarily on reducing long-term average or short-term average ambient PM concentrations.

Table 1: Estimated effects of air pollution on daily mortality and hospital admissions from APHEA2 and NMMAPS studies

	Study	
	APHEA2	NMMAPS
Increase in total deaths per 10 μg/m^3 PM_{10} (95% confidence limits)	0.6% (0.4 – 0.8%)	0.5% (0.1 – 0.9%)
Increase in COPD (APHEA2: COPD + asthma) hospital admissions in persons > 65 yrs per 10 μg/m^3 PM_{10} (95% confidence limits)	1.0% (0.4 – 1.5%)	1.5% (1.0 – 1.9%)

The APHEA2 mortality study covered a population of more than 43 million living in 29 European cities, which were all studied for > 5 years in the early-mid 1990s.

The APHEA2 hospital admission study covered a population of 38 million living in 8 European cities, which where studied for 3 to 9 years in the early-mid 1990s.

The NMMAPS mortality study covered a population of more than 50 million living in 20 metropolitan areas in the United States of America, which were all studied over the 1987–1994 period.

The NMMAPS hospital admission study covered 10 large metropolitan areas in the United States of America with a combined population of 1 843 000 subjects over 65 years old.

6 Ozone (O_3)

6.1 Introduction

Ozone is the most important photochemical oxidant in the troposphere. It is formed by photochemical reactions in the presence of precursor pollutants such as NO_x and volatile organic compounds. In the vicinity of strong NO_x emission sources, where there is an abundance of NO, O_3 is "scavenged" and as a result its concentrations are often low in busy urban centres and higher in suburban and adjacent rural areas. On the other hand, O_3 is also subject to long-range atmospheric transport and is therefore considered as a trans-boundary problem.

As a result of its photochemical origin, O_3 displays strong seasonal and diurnal patterns, with higher concentrations in summer and in the afternoon. The correlation of O_3 with other pollutants varies by season and location.

There is evidence from controlled human and animal exposure studies of the potential for O_3 to cause adverse health effects. Epidemiological studies have also addressed the effects of short and long-term exposures to O_3 and provided important results. However, the health effects of O_3 have been less studied than those of PM and thus more research is needed, especially addressing the spatial and seasonal patterns and misclassification of individual exposure in association with health outcomes.

6.2 Answers and rationale

1) Is there new scientific evidence to justify reconsideration of the current WHO Guidelines for ozone (O_3)?

Answer:

The current WHO Air quality guidelines (AQG) (WHO, 2000) for O_3 provide a guideline value of 120µg/m^3 (60 ppb), based on controlled human exposure studies, for a maximum 8-hour concentration. The AQG also provide two concentration-response tables, one for health effects estimated from controlled human exposure studies and one from epidemiological studies. No guideline for long-term effects was provided. Since the time these guidelines were agreed, there is sufficient evidence for their reconsideration. Issues to be considered are: the averaging time(s) for the short-term guidelines and their associated levels, the concentration-response functions used in the tables, the outcomes included in the concentration-response tables, whether a long-term guideline and/or complementary guidelines (e.g. restricting personal activity) should be adopted.

Recent epidemiological studies have strengthened the evidence that there are short-term O_3 effects on mortality and respiratory morbidity and provided further information on exposure-response relationships and effect modification. There is new epidemiological evidence on long-term O_3 effects and experimental evidence on lung damage and inflammatory responses. There is also new information on the relationship between fixed site ambient monitors and personal exposure, which affects the interpretation of epidemiological results.

Rationale

Since 1996 several epidemiological studies assessed the short-term effects of O_3 on various health outcomes. Based on a meta-analysis of studies published during the period between 1996 and 2001 on short-term effects of O_3 on all non-accidental causes of death in all ages (or older than 65 years), significant increase of the risk of dying (between 0.2 % and 0.6 % per each increase in 10 μg/m^3 or 5 ppb) was shown (210) whatever the lag period, the season of study or the timing of the ozone measurement (Table 2). In some instances, the effects coefficients observed were higher in places with low O_3 concentrations. This may be a reflection of a curvilinear concentration – response, or of other specific characteristics of populations where influential studies were done (see also rationale to question 3). Studies limited to the summer season tend to reveal a larger effect, while the strength of the effect increases with longer average times (> 1 hour) of O_3 measurement. Estimates remained very similar if studies using Generalized Additive Models (GAM) were excluded to avoid a possible bias which has recently been reported (31). In addition, a large multi-centre study from the United States of America, the NMMAPS study, reported a significant effect of O_3 during the summer season, of 0.41 % increase in mortality associated with an increase of 10 ppb (20 μg/m^3) in daily O_3 concentrations at lag 0 (i.e. the same day). A larger effect was found at lag 2 (levels two days earlier), independently of other pollutants (27, 211). Ozone daily levels were associated with hospital respiratory admissions at all ages in most of the studies using 8-hour measures (Table 2) and also in many of the studies using other averaging periods. The magnitude of the association was slightly larger than that obtained for mortality (0.5 to 0.7 % increase in admissions per increase of 10 μg/m^3 or 5 ppb in O_3; Table 2). There are very few studies reporting data on lag 0. Studies on admissions for asthma in children did not find conclusive associations with any O_3 measurement. However, there is evidence that during days when ozone levels are high, asthmatic subjects increase their use of medication (212) that may mask any adverse O_3 effect (213).

It should be noted that O_3 usually displays a strong seasonality (with a summer peak), which is different from the seasonal patterns of other pollutants and of the above health outcomes. Therefore, if careful control of seasonal patterns is not applied, the effect of O_3 is underestimated (and may appear protective). All the above studies have allowed for seasonal adjustment in various ways.

In addition, all studies reported from 1996 and 2001, which give estimates of O_3 effects on lung function measures were considered (210). The estimates were grouped by the subjects' characteristics but there was a mixture of lags and averaging times. Therefore, summary estimates are not provided (Table 3). Overall, the majority of studies showed a negative impact of acute effects of O_3 on lung function.

Some epidemiological studies on long-term effects of O_3 have been published during the period from 1996 to 2002, giving some evidence of long-term effects on various health endpoints. These studies are discussed in more detail in the rationale to question 2.

New data from experimental studies have not contributed much additional evidence for O_3 effects at current ambient levels. Results from experimental studies show the potential of O_3 exposure to cause effects and have provided some insights to underlying mechanisms. Some of the most relevant findings of these studies are presented below. In interpreting these, it is important to note that only healthy or mildly asthmatic subjects were included in the study populations.

From a controlled exposure study (214) in healthy and allergic asthmatic nonsmokers there is evidence of lung function decrements after 3 hrs of exposure to either 100 μg/m^3 of H_2SO_4 or

NaCl (control) aerosol followed by 360 µg/m^3 (180 ppb) of O_3, with greater decrements for those exposed to H_2SO_4. Repeated daily, short term exposures of healthy and mildly asthmatic subjects to O_3 attenuates the acute lung function and, to a less extent the inflammatory response, reaching a maximum over 3 to 5 days and with a recovery over four to seven days after the end of the exposure (215, 216, 217, 218, 219, 220). Bronchoalveolar lavage demonstrates that mucosal damage and inflammation continue despite adaptation documented by lung function and clinical assessment (220, 221).

Since the last WHO evaluation new non-invasive tests have become available in both humans and animals allowing non-invasive exploration of lung damage and inflammation not only under controlled exposures studies but also under field conditions on subjects exposed to ambient O_3 (222). These tests include the assay in serum of lung-specific proteins to detect lung epithelium permeability changes or the analysis of inflammatory markers in exhaled air or in the condensates of exhaled breath condensate. Compared to lung lavage techniques and other tests of lung damage, these non-invasive tests present several advantages, such as sensitivity, repeatability, non-invasiveness and applicability in field studies. In particular, they allow for monitoring of lung inflammation or damage induced by ambient O_3, especially in sensitive groups such as children.

There is evidence for a significant association between short-term peaks in ambient air concentrations of O_3 and lung epithelial damage (222) as measured by the intravascular leakage Clara cell protein (CC16). Other studies in humans have shown that spirometric variables show adaptation in young adults; and persistent small airway dysfunction/resistance (0.25 ppm for 2 hours over 4 days) (223) and that repeated exposure (0.125 ppm for 2 hours over 4 days) of allergic asthmatics enhances progressively both functional and inflammatory, bronchial responses to inhaled allergen challenge (224), see also Table 4.

Studies in animals undergoing controlled exposures to O_3 have also shown various biological responses at different schemes and levels of exposure (225, 226, 227).

A discussion of the relationship between fixed site ambient monitors and personal exposure can be found in the rationale to Question 9.

2) Which effects can be expected of long-term exposure to levels of O_3 observed currently in Europe (both clinical and pre-clinical effects)?

Answer:

There are few epidemiological studies on the chronic effects of ozone on human health. Incidence of asthma, a decreased lung function growth, lung cancer and total mortality are the main outcomes studied. At levels currently observed in Europe, the evidence linking O_3 exposure to asthma incidence and prevalence in children and adults is not consistent. Available evidence suggests that long-term O_3 exposure reduces lung function growth in children. There is little evidence for an independent long-term O_3 effect on lung cancer or total mortality.

The plausibility of chronic damage to the human lung from prolonged O_3 exposure is supported by the results of a series of chronic animal exposure studies.

Rationale:

Incidence of asthma was studied in adults (228), in California in the AHSMOG (Adventist Health Smog) study. A cohort of 3 091 non-smokers, aged 27 to 87, was followed over15 years (1977 to 1992). For males, a significant relationship between reports of doctor diagnosed asthma and 20-year mean 8-hour average ambient ozone concentration (relative risk = 2.09 (1.03–4.18)) for an inter-quartile range of 54 µg/m^3 (27 ppb) was found. Use of alternative O_3 metrics, such as hours above a certain level, showed the strongest effect in relation to the mean ozone concentration, followed by 8-hour average concentration and then by hours exceeding a certain threshold value. No relationship was observed in females. Adjustment for other pollutants did not diminish the strength of the relationship. The prospective nature, a small loss to follow-up and a detailed measure of the cumulative air pollution exposure (incorporating accurate individual interpolations using residence and work location (229) strengthen the validity of these results. The small number of cases (32 males and 79 females), a potential misclassification of self-reported diagnosis, an imprecise time-pattern in the measures of outcome and past-exposure (residence was measured three times in 15 years), and a lack of consistency between the two genders undermines the validity of results. Hence, low quality of outcome diagnosis might not allow a clear distinction between incidence and exacerbation. Although gender differences were not among the prior hypotheses but were a result of subgroup analyses, the lack of effect in females could be a phenomenon due to a differential exposure by gender.

In a cohort study of 3 535 children, aged 10 to 16 years with no history of asthma recruited in 12 communities in the Southern California study and followed during 5 years, the relative risk of developing asthma among children playing three or more sports (8 % of the children) was 3.3 (1.9–5.8) compared with children playing no sports in communities with high ozone concentrations (four year average of 112 µg/m^3 to 138 µg/m^3 (56 to 69 ppb)), but not in communities of low ozone (230). This effect modification of ozone was not seen for the other standard pollutants. The longitudinal nature of the study and the low proportion of subjects lost during follow-up strengthen these results. In the same study in Southern California, prevalence of asthma was not associated with ozone levels among the 12 studied communities (231). On the contrary, prevalence of asthma increased with average levels of O_3 among the 2 445 13 to 14 year-old children of 7 communities participating in the French ISAAC study (International Study on Childhood Asthma and Allergy) (232), and among the 165 173 high school students aged 11 to 16 from 24 areas in the Taiwan ISAAC study (233), but in the French study, analysis at the individual level did not show an association. However, difficulties in diagnosis of asthma using self-reporting of symptoms and limitations of prevalence studies with no control of in/out migration could explain these differences.

Lung function growth was studied in three prospective studies with repeated measures in the same subjects. In nine areas without major industrial sites in Austria, 1 150 children aged 8 to 11 were followed during 3 years (1994–1997) performing 6 lung function tests (234). The change in lung function (FVC, FEV1 and MEF50) between the pre and post-summer test was negatively associated with the O_3 mean concentration (with a personal interpolation). A 10 ppb (20 µg/m^3) difference in average O_3 exposure was associated with a small but significant predicted decrement of 2 %. The wintertime change in O_3 was also negatively associated with the lung function change, but the association was weaker. The use of peak O_3 concentrations instead of average O_3 levels resulted in a non-significant association. The analysis of only those children who did not change their town of residence increased the association. Presence of asthma did not modify this association. A further analysis showed the effect of O_3 to be independent of particles and nitrogen dioxide (235).

These results were not replicated by the first of the Southern California cohort studies (22). More than 3 000 children from 12 communities around Los Angeles were followed during 4 years (from 1993 to1997) and lung function tests were performed annually. A negative effect of O_3 on lung growth was not observed. A low variation of O_3 and a high variation in particulate matter among these Californian communities could explain the lack of the effect. However, a second study following 1 678 children of nine to ten years from 1996 to 2000 in the same 12 communities showed that exposure to O_3 (expressed as the annual average of the concentration between 10 a.m. and 6 p.m.) was associated to reduced growth in peak flow rate (PEF), as well as to FVC and FEV1 growth among children spending more time outdoors (23). However, there was a greater negative association with acid vapours, NO_2, and $PM_{2.5}$ than for O_3 in this cohort. The repeated measures among the same children give more validity to these studies than to the cross-sectional studies.

Cross-sectional studies are not fully consistent. In the same study in South California, lung function level was lower in communities with higher ozone in comparison to communities with lower O_3 average levels, particularly among girls with asthma and spending more time outdoors (236). In a study on 24 communities in the United States and Canada among 10 251 children between the age of 8 and 12 a negative association with several O_3 exposure metrics was found for FVC and FEV1, although the association with FVC was reduced after adjustment for strongly acidic particles. O_3 and acidic particles were highly correlated in the study areas (78).

Among adults, in the 1 391 non-smokers of the AHSMOG study a decrement of FEV1 in relation to cumulative O_3 exposure was observed in males whose parents had asthma (237), as well as in a sample of 130 UC Berkeley freshmen (238), while an association between O_3 and lung function was not found in the 9 651 adults residing in the eight areas of the SAPALDIA study (Swiss study on air pollution and lung diseases in adults) (93). However, this study did not have adequate power to assess the O_3 effect (range of long-term O_3 average was 31 to 51 $\mu g/m^3$ or 15.5 to 25.5 ppb).

Symptoms of bronchitis did not increase in children from communities with higher levels of O_3 among the 3 676 children participating in the south California study (88), as they similarly did not increase among the 9 651 adults in the Swiss communities with higher O_3 participating in the SAPALDIA study (94).

Lung cancer both incidence (239) and mortality (9) was strongly associated with long-term concentrations of ozone among males of the 6 338 non-smoking adults participating in the AHSMOG study and followed from 1977 to 1992. Differences in exposure to O_3 (males in the study spent more time outdoors) could explain the gender differences. It was difficult to separate the effect from ozone and particles, since a similar association was obtained with particles and correlation between particles and ozone was high (9). The ACS cohort study (13) did not find any association of long-term O_3 exposure and lung cancer or total mortality.

The plausibility of chronic damage to the human lung from prolonged O_3 exposure is supported by the results of a series of chronic animal exposure studies, especially those in rats (240, 241) using a daily cycle with a 180 ppb ($360\mu g/m^3$) average over nine hours superimposed on a 13-hr base of 60 ppb ($120\mu g/m^3$), and those in monkeys of Hyde et al. (242) and Tyler et al. (243) applying 8 hours per day of 150 and 250 ppb (300 and $500\mu g/m^3$). The persistent cellular and morphometric changes produced by these exposures in the terminal bronchioles and proximal alveolar region and the functional changes are consistent with a stiffening of the lung reported by Raub et al, (244) and Tyler et al. (243).

3) Is there a threshold below which no effects on health are expected to occur in all people?

Answer:

There is little evidence from short-term effect epidemiological studies to suggest a threshold at the population level. It should be noted that many studies have not investigated this issue. Long-term studies on lung function do not indicate a threshold either. However, there may well be different concentration-response curves for individuals in the population, since in controlled human exposure and panel studies there is considerable individual variation in response to O_3 exposure. From human controlled exposure studies, which generally do not include especially sensitive subjects, there is evidence for a threshold for lung damage and inflammation at about 60 to 80 ppb (120–160 ug/m3) for short-term exposure (6.6 hours) with intermittent moderate exercise. Where there are thresholds, they depend on the individual exercise levels.

Rationale

For epidemiological studies of short-term effects, the acute association with mortality for all causes has been shown in studies carried out in places with low mean O_3 levels such as London (245) suggesting a lack of a threshold effect. There is no obvious trend towards larger associations in places with higher O_3 levels. For example, the association found in Mexico City (246) was relatively small in magnitude (although still significant). This may suggest a lack of a threshold. These paradoxical phenomena of a lower association in places with higher levels could be explained by other factors such as adaptation; occurrence of protective factors such as diet; the lower levels of other pollutants or modified activity patterns which often occur when ozone concentrations are high or fewer competitive risks such as a higher mortality due to infectious diseases.

Most studies do not explicitly describe the shape of the concentration-response function. Some studies suggest a curvilinear association, including one recently conducted in Canada (247) that suggested an inflexion to a steeper slope above around 25 $\mu g/m^3$ (13.5 ppb) as 24-hour average. Wong et al (248) in Hong Kong found a slight increase above about 40 $\mu g/m^3$ (20ppb) as 8-hour average and Hong et al (249) in Korea a steeper increase above about 46 $\mu g/m^3$ (23 ppb) (also 8-hour average). Hoek et al (250) found a chi-squared test for non-linearity was not significant and that there was little change in slope until all days above 30 $\mu g/m^3$ (15 ppb) as 24-hour average had been removed. However, extrapolating from single studies has limitations, in comparison with meta-analysis. In addition, many of the concentration-response functions suggesting thresholds are for single pollutant models and confounding by other pollutants may vary across the concentration range.

Concentration-response curves are also rarely described explicitly in studies on respiratory hospital admissions. A study in London suggested a threshold around 80 to 100 $\mu g/m^3$ (40 to 50 ppb) as 8-hour average (251) but other studies have shown linear associations (252).

In panel studies, significant negative effects on lung function have been found after omitting days above 120, 100 or even 80 $\mu g/m^3$ (60, 50 and 40 ppb) (1-hour average) (253, 254, 255) although in the latter 2 studies exercise levels were quite intense (cyclists and farm workers). Some studies suggest a curvilinear relationship with a threshold at quite low ozone concentrations (e.g. Korrick et al. (256) around 80 $\mu g/m^3$ (40 ppb) as 8-hour average and others find linear relationships across the whole range, e.g. Higgins et al (257) for a range of 12 to 54

µg/m^3 (24-hour average). At low O_3 concentrations, the mean decreases in lung function are small and may not be clinically significant, but individuals may still experience meaningful decreases.

For healthy young adults, the thresholds for the short-term effects of O_3, as evaluated by spirometry markers of lung damage and inflammation, lie below 160 µg/m^3 (80ppb), based on the effects observed in a series of controlled 6.6 hour human exposure studies at concentrations of 160, 200, and 240 ug/m^3 with intermittent moderate exercise (221, 258, 259, 260, 261).

Long term Effects: An increase in asthma incidence in the AHSMOG study occurred when comparing the effect of the O_3 exposure in the lowest tertile of 70 µg/m^3 (35 ppb, as 8-hr average) with the second tertile (relative risk, RR = 4.4), and the magnitude of the association did not increase when comparing the first and the third tertile (RR = 4.0) (228) again suggesting a lack of threshold, or an effect at low exposures. The 70 µg/m^3 (35 ppb) level in the AHSMOG study is lower than the median level of 102 µg/m^3 (51 ppb) that was observed in the South California study that separated communities with and without an effect of sport on asthma incidence (230). In an Austrian study (234) on lung function growth the annual O_3 concentration was lower than in California, ranging from 36 µg/m^3 (18 ppb) to 81 µg/m^3 (40.7 ppb) with an average summertime O_3 of 70 µg/m^3 (35 ppb) and a standard deviation of 17 µg/m^3 (8.7 ppb). The best fitting dose-response function on the association between O_3 and lung function in the Austrian study was a linear model, suggesting again a lack of a threshold level. Hence, the decrease in FEV1 did not vary when only exposures below the median of O_3 exposure of 57 µg/m^3 (28.6 ppb) were selected (-0.014) compared to when only levels above the median were chosen (-0.015). In the South California study (23) only linear models were tested, and other forms of the dose-response curve or the occurrence of threshold could not be evaluated.

4) Are effects of O_3 dependent on subjects' characteristics such as age, gender, underlying disease, smoking status, atopy, education, etc.?

Answer

Individuals vary in their O_3 responsiveness for different outcomes, for reasons which remain largely unexplained but appear to be partly based on genetic differences. There is some evidence that short-term O_3 effects on mortality and hospital admissions increase with age. Gender differences are not consistent. It appears that the effects of O_3 exposure on symptoms are greater in asthmatic children. Lung function decrements are more consistent in asthmatic children, especially those with low birth weight.
One important factor modifying the effect of O_3 on lung function is ventilation rate. As tidal volume increases, O_3 penetrates deeper into the lungs. Duration of exposure is also a critical factor: Ozone effects accumulate over many hours but after several days of repeated exposures there is adaptation in functional but not inflammatory responses. The effects of O_3 exposure on lung function, symptoms and school absences are larger in children who exercise more or spend more time outdoors.

Rationale
In two studies, the effect of O_3 on daily mortality has been higher in persons older than 65 years (247, 262). There are very few time-series studies on mortality that have addressed effects in persons younger than 65 to allow confirmation of this finding. In the meta-analysis of time series studies on emergency admissions for respiratory causes, there was a pooled positive association

with all respiratory admissions at all ages (mainly including old people) while there was no association for studies with asthma in children (210), probably reflecting that the risk of O_3 effect increased with age. By contrast, lung function decrements attributable to O_3 have been much greater in children and young adults than in older adults (263).

Data from the National Cooperative Inner-City Asthma study (NCICAS) in the United States were analysed to identify susceptible subgroups (264). In a panel of 846 asthmatic children, morning peak-flow decrease and incidence of symptom increase were associated with O_3 exposure in children with low birth weight or premature birth. In another study in children in Australia, children with doctor-diagnosed asthma or bronchial hyper-reactivity were at higher risk of functional responses (265). In the meta-analysis of acute effects on lung function, the negative effect of O_3 on peak flow rates was more consistent among studies only including children with asthma compared to studies including general population children or healthy children, but the size of the association in some of the latter studies was even larger than in studies including only asthmatics (Table 3). Finally, the Southern California Children's Health study shows that children exercising more (230) and children spending more time outdoors (23) are at higher risk of an effect of O_3 on asthma incidence and decrease of lung function growth, respectively.

Results on gender differences are not consistent. In the AHSMOG study in adults and the NCICAS study in children, long-term effects of O_3 for several outcomes were only seen in males (9, 228, 237, 264). In both studies, this effect was attributed to a larger time spent outdoors by males, which was observed in the AHSMOG study. In contrast, the geographical comparison of lung function levels among the children participating in the Southern California study showed a larger effect of O_3 among girls with asthma (236) although they stayed less time outdoors and less time exercising than boys. In general, a higher exposure might explain why boys are usually at higher risk of asthma symptoms and male adults at a higher risk of all respiratory effects. The gender and racial differences, when adjusted for lung capacity, if any, are much smaller (266, 267). Overall, it is debatable if there are gender differences of O_3 effects on lung function and respiratory diseases.

Persons with underlying respiratory diseases have been found to have greater responsiveness to O_3 associated function changes in some controlled exposure studies (268, 269), but not in others (270, 271). However, controlled exposure studies have involved only subjects with very mild disease. "Healthy" smokers tend to be less responsive than non-smokers (272), but this effect of smoking falls over time after successful smoking cessation (273). There are no data on the influence of education or other socio-economic variables on O_3 associated changes in respiratory function.

Other short-term responses to the inhalation of O_3 have been investigated primarily in healthy, non-smoking young adults. These effects of O_3 include: increases in lung inflammation (261, 269, 274); lung permeability (275); respiratory symptoms (258, 276)); and decreases in mucociliary clearance rates (277). Little is known about the influence of age, gender, underlying disease, smoking status, atopy or education and other socio-economic variables on these responses to O_3.

A critical factor affecting O_3 deposition and the induction of short-term functional responses is the duration of the exposure. O_3 is a lower-lung irritant and effects accumulate over many hours. However, after several days of repetitive exposures, there is an adaptation that leads to a reduced respiratory functional responsiveness which lasts for a week or more (217, 278). While there is an adaptation at least in the larger airways, it does not seem to involve the functional responsiveness at the site of maximum O_3 injury, i.e. respiratory bronchioles (223), and the lung

inflammation responses (274). In any case, those responsive on one occasion are fairly reproducibly responsive when similarly exposed to O_3 (279).
It is also noteworthy that individuals vary in their overall functional responsiveness to O_3. For a group of 20 to 30 individuals exposed to 160 to 240 $\mu g/m^3$ (80 to 120 ppb) of O_3 for 6.6 hrs while undergoing moderate exercise for 50 min each hr, there would be significant average decrements in lung function and significant average increases in symptoms and inflammatory cells in lung lavage, ranging between individuals from little or none in some of them to major changes in others. However, those who responded in terms of one endpoint did not necessarily respond in terms of the others. This is not unexpected, when the different mechanisms that underlie the responses are taken into account (e.g., inhibition of deep inspiration related to neurokinins and alterations in small airway function related to damage to respiratory bronchioles). Thus, the critical host characteristics for functional responses remain unknown and there are, as yet, no biomarkers that can reliably predict responsiveness in humans. It has been suggested that intrinsic narrowing of the small airways may be a significant component of the functional response (280).

5) To what extent is mortality being accelerated by long- and short-term exposure to O_3 (harvesting)?

Answer:

Long-term O_3 effects have been studied in two cohort studies. There is little evidence of an independent long-term O_3 effect on mortality so that no major loss of years of life is expected. The issue of harvesting, i.e. the advancement of mortality by only relatively few days, has not been addressed in short-term exposure studies of O_3.

Rationale:
For the long-term effects of O_3 see the answer and rationale to Question 2. In short-term studies, the issue of harvesting, i.e., the advancement of mortality by only few days has not been studied for O_3 effects. A few studies have addressed this issue for the effects of PM_{10} or $PM_{2.5}$ and it was found that mortality displacement was substantial for most causes of death and harvesting could not explain all the excess mortality (see also answer and rationale to question 5 in the PM section). Whether there are also persistent effects of O_3 as well, has not been determined.

6) Is O_3, per se, responsible for effects on health?

Answer:

In short-term studies of pulmonary function, lung inflammation, lung permeability, respiratory symptoms, increased medication usage, morbidity and mortality, O_3 appears to have independent effects (especially in the summer). For long-term effects the results are not entirely consistent. When particle acidity was studied, O_3 effects were partly explained. A few studies in North America found effects of O_3 on asthma incidence and functional changes independent of other classical pollutants, but acidity was not taken into account.

Experimental studies show the potential of O_3 to cause these health effects.

Rationale:
Several short-term mortality studies adjusted O_3 for particles, after including multiple pollutants in the same regression model. For a meta-analysis (210), 18 studies including O_3 and particles in the same models were selected (including studies carried out in all seasons or summer and with various lag periods). Almost all estimates were positive (14 out of 18; 10 with a $p<0.05$), while only 2 were negative (and statistically not significant) and summarized estimates are very similar to those obtained without adjustment. These findings coincide with results from the NMMAPS study in 90 North-American cities during the summer. Adjustment for sulfate, SO_2 or NO_2 was done rarely, though in the few studies that incorporated these pollutants, the association of O_3 was not modified after including the other pollutants in the regression model (247, 281, 282). For the effects reported to be associated with ambient O_3 in population-based excess frequencies, the answer is less clear-cut, and other components in photochemical smog that elicit reactive oxygen species (ROS) in the cardiopulmonary system may also play a role. For hospital and emergency department respiratory admissions, O_3 appears to be more influential than other pollutants that may have either additive or synergistic effects based on stronger association in multiple pollutant model analyses. However, emergency and hospital admissions are metrics that differ widely between countries. On the other hand, for excess daily mortality, O_3 appears to have a lesser effect than fine particles ($PM_{2.5}$).

In some of the long-term studies that adjusted for other classical pollutants (PM_{10}, $PM_{2.5}$, SO_4, NO_2 and SO_2), O_3 effects on incidence of asthma were independent (228, 230). Similarly, some studies on lung function growth also have adjusted for other pollutants and found that O_3 had independent effects on several functional markers (22, 23, 235). In the UC Berkeley study, lifetime O_3 exposure was negatively associated with mid and end-expiratory flows even after adjusting for particles and NO_2 (238). In the study of the 24 cities (78) adding particle acidity concentration in a two-pollutant model reduced the effect of daily mean O_3 on FVC (although a negative effect of O_3 persisted). However, the study was designed to measure effects of acidity, and levels of O_3 among communities were probably not sufficiently heterogeneous. For the functional and symptom responses, which have been identified in both controlled exposure studies and in field studies at comparable concentrations of O_3 the observed effects can be clearly attributed to O_3 per se.

Finally, the case of lung cancer appeared different since in the AHSMOG study there was a strong correlation between particulate matter and O_3, and a similar association in the single pollutant models was observed for particulate matter and for O_3. The American Cancer Society Study (13) did not implicate O_3 in the long-term effects on mortality.

7) For PM: which of the physical and chemical characteristics of particulate air pollution are responsible for health effects?

Not relevant for ozone.

8) What is the evidence of synergy/interaction of O_3 with other air pollutants?

Answer:

Epidemiological studies show that short-term effects of O_3 can be enhanced by particulate matter and vice versa. Experimental evidence from studies at higher O_3 concentrations shows

synergistic, additive or antagonistic effects, depending on the experimental design, but their relevance for ambient exposures is unclear. O_3 may act as a primer for allergen response.

Rationale:
Synergy between O_3 and particles (or other pollutants) has been measured in very few epidemiological studies. In a follow-up of more than 2 000 children during the first 6 months of 1996 in the Southern California Children's Health Study (283), the short-term effect of O_3 on school absenteeism was stronger in periods with low particulate levels than with high particulate levels. In the APHEA2 study (284) the effect of daily particle concentrations on respiratory hospital admissions among those over 65, was stronger in areas with high O_3 levels.

The evidence based on studies comparing the functional decrements induced by exposures to O_3 in combination with acid aerosols and NO_2 in ambient air to those induced by O_3 as a single pollutant in inhalation chambers (253) suggest a synergism of O_3 with the co-pollutants at levels known not to produce significant effects as single pollutants in controlled exposures. Frampton et al. (214) have shown a synergistic functional effect of O_3 with H_2SO_4 in controlled exposures of both healthy and asthmatic subjects.

The best evidence for synergy between O_3 and other pollutants like NO_2 or H_2SO_4 comes from controlled short-term exposures in laboratory animals, that have generally been made at concentrations much higher than those occurring in recent years in ambient air. The endpoints considered include lesions in the gas-exchange region of the lungs, enzyme activities etc. However, the effects can be synergistic, additive, or antagonistic, depending on the combination of the pollutants and their concentrations (227), exposure regimen (concomitant or sequential) as well as on the health endpoints considered. The pollutant combinations studied include O_3 with H_2SO_4, $(NH_4)_2SO_4$, HNO_3, HCHO or cigarette smoke.

There is evidence that O_3 exposure potentiates the functional and inflammatory responses to inhaled allergen in subjects with pre-existing allergic airway disease (Jorres et al, 1996; Holz et al, 2002 (224, 285).

9) What is the relationship between ambient levels and personal exposure to O_3 over short and long periods (including exposures indoors)? Can the differences influence the results of studies?

Answer:

Personal exposure measurements are not well correlated with ambient fixed site measurements. To account for that, in some studies, additional information (e.g., activity patterns) was used to improve personal exposure estimates based on fixed site measurements. Being a highly reactive gas, O_3 concentrations indoors are generally lower (less than 50%) than those in ambient air. There are very few indoor sources in most homes (such as xerographic copiers, electrostatic air cleaners). Outdoor O_3 levels vary across city areas because O_3 is scavenged in the presence of NO. Early morning and late night exposures outdoors are lower because of the diurnal cycle of ambient O_3. Thus, for O_3, cumulative daily or long-term average exposures are largely determined by exposures occurring outdoors in the afternoon. The studied effects of exposure misclassification are in the direction of underestimation of O_3 exposure effects and may conceal real effects.

Rationale

The spatial variability of ozone levels may be low within large areas. This is obviously an obstacle in designing epidemiological studies built on differences in exposure of different communities, but favours the use of fixed site monitors to characterize exposure levels for large populations, both in studies with spatial and temporal contrast. However, there are gradients within cities, due to the reaction of ozone with NO emitted from traffic and other combustion sources. There may even be a substantial variation between neighbouring residential areas, as measured by front-door samples (286). In addition, there is a strong diurnal variation, with the highest levels usually in the afternoon. Further, ozone levels are commonly much lower indoors than outdoors. Short-term personal exposure measurements are thus not well correlated with ambient fixed site measurements (286). The use of outdoor ozone concentration from fixed site monitors, as a measure of short-term ozone exposure in epidemiological studies, may, therefore, result in misclassification error, both in studies with temporal or spatial contrasts.

However, the temporal correlation was in one study found to vary among subjects, due to the activity pattern, geographical variables, home variables such as ventilation and the distance from the monitoring station and traffic (287). In spite of the poor temporal correlation on the individual level, in the largest follow-up study on O_3 exposure, the differences in average levels between communities were similar when outdoor measurements or personal measurements were used, but only during the ozone season, which is warm. The reason for this is probably that people spend more time outdoors and that the differences between outdoor and indoor levels are smaller, due to open windows. This finding is relevant for studies on long-term effects since – during the warm season – the outdoor measurement provides a valid estimate of the spatial variation provided time spent by subjects in the different areas was measured (288). It has also been shown that (128, 248, 288) having air conditioning decreases the personal O_3 exposure level, and also its correlation with outdoor measurements. Most of these random misclassification effects cause true effects to be interpreted as less strong (100). It is, however, possible that the exposure errors are correlated to the exposure level, which would lead to a positive or negative bias. Systematic errors may also occur in studies of urban areas where the ozone levels are substantially lower in the city centres (spatial error). A few epidemiological studies have explicitly assessed the consequences of the poor correlation between personal exposure and the commonly used ozone levels measured at fixed sites. The misclassification error was found to bias the effect estimates towards the null hypothesis (289, 290).

Some of the studies on the long-term effects have tried to reduce spatial or temporal error by incorporating additional information to the outdoor measurements. In the AHSMOG study, individual cumulative exposure was calculated using monthly measurements from air monitoring stations in California, and distance from residence and work to the stations. This interpolation method was found to increase the validity of the exposure estimates (229). One Austrian study also calculated an individual ozone concentration weighting the outdoor measurements by the time spent in the area (234).

10) Which are the critical sources of the pollutant responsible for health effects?

Answer:

Ozone is a secondary pollutant produced by photochemical activity in the presence of precursors. The working group felt that it was beyond its core competence to give a detailed description of ozone formation and dispersion patterns.

Rationale
Ozone is formed in the troposphere by photochemical reactions in the presence of precursor pollutants such as NO_x and volatile organic compounds. Where there is an abundance of NO, O_3 is "scavenged" and as a result its concentrations are often low in busy urban centres and higher in suburban areas. O_3 is also subject to long-range atmospheric transport and may be considered as a trans-boundary problem.

11) Have positive impacts on public health of reductions of emissions and/or ambient concentrations of O_3 been shown?

Answer

There are very few opportunities to evaluate O_3 reduction per se. One study of intra-state migrants showed a beneficial effect on lung function in children who moved to lower PM and O_3 areas. A decrease in O_3 during the 1996 Olympics was associated with a reduction of asthma admissions. The interpretation of these findings is unclear.

Rationale
Emission reductions of O_3 precursors (NO_x and volatile organic compounds) can result in lower concentrations of not only NO_2 and O_3, but in fine particles ($PM_{2.5}$) as well. Without the oxidants generated in the photochemical reaction sequences, there would be a reduction in the oxidation of SO_2 and NO_2, which leads to acidic sulfate and fine particles and nitric acid vapour, as well as less formation of organic fine particles. Therefore an assessment of the beneficial effect of reducing O_3 only is difficult.

Children in the Southern California cohorts who moved from communities with relatively high PM and O_3 concentrations to communities with lower concentrations had better lung function growth than children who remained in those communities (24), while children who moved from communities with relatively low $PM_{2.5}$ and O_3 concentrations to communities with higher $PM_{2.5}$ and O_3 concentrations had lesser lung function growth than those who remained in the cleaner communities. However, it is not clear whether this results is due to changes in O_3 or PM. Friedman et al (291) took advantage of a natural experiment associated with a decrease in O_3 exposure in Atlanta during the 1996 Olympics and demonstrated that acute O_3 effects to asthma admissions were substantially reduced. In other air pollution situations the beneficial effects mainly of reducing particulate matter (203) and SO_2 (292, 293) have been demonstrated. More research is needed in that area but the appropriate settings are few.

12) What averaging period (time pattern) is most relevant from the point of protecting human health?

Answer:

For short-term exposure, it is clear that the effects increase over multiple hours (e.g., 6–8 hours for respiratory function effects and lung inflammation). Thus, an 8-hour averaging time is preferable to a 1 hour averaging time. The relationship between long term O3 exposure and health effects is not yet sufficiently understood to allow for establishing a long-term guideline.

Rationale:

From controlled human exposure studies it appears that the effects increase over multiple hours (258, 261, 263). The evidence from epidemiological studies is not conclusive, because in practice there is a strong correlation between the different measures. The association of O_3 exposure with long-term effects is not yet clear enough to justify recommending a long-term standard (see Rationale to Question 2).

Table 2: Summary of meta-analysis of time-series studies published during the period 1996–2001. **Note** that an updated meta-analysis also involving more recent studies is being performed in spring 2003. See also the recommendations in chapter 8. Only the results of the updated meta-analysis should be used for any health impact assessment.

CAUSE	SEASON	LAG	TIMING	Nº STUDIES		RANDOM EFFECTS SUMMARY COEFFICIENT ‡
				RR > 1	RR < 1	
Mortality	ALL	0	1 hour	13 (8*)	3 (0)	0.2 (0.1–0.3)
			8 hours	9 (5*)	3 (0)	0.4 (0.2–0.5)
			24 hours	8 (5*)	3 (1*)	0.4 (0.1–0.6)
		select†	1 hour	17 (13*)	3 (0)	0.3 (0.2–0.4)
			24 hours	22 (8*)	3 (0)	0.4 (0.3–0.6)
	SUMMER	any	1 hour	6 (5*)	1 (0)	0.4 (0.1–0.6)
			8 hours	6 (5*)	1 (0)	0.6 (0.3– 0.9)
			24 hours	2 (2*)	0	–
Hospital admissions respiratory	ALL	select	1 hour	4 (2*)	1 (0)	0.5 (0.1–1.0)
			8 hours	10 (6*)	1 (0)	0.7 (0.3–1.0)
			24 hours	6 (2*)	1 (0)	0.6 (0.2–1.0)
Asthma admissions in children	ALL	select	1 hour	3 (0)	1 (0)	0.1 (-0.4, 0.6)
			8 hours	4 (2*)	3 (2*)	0.1 (-1.2, 1.3)

* number of single studies with a $p<0.05$
† "selected" lag = If results for more than one lag were presented the lag selected was chosen as: lag focused on by the author, most statistically significant or largest estimate.
‡ Percentage change per 10 ug/m^3 increase and (95% confidence interval), preliminary results

References used in the meta-analysis:

ALL-CAUSE MORTALITY PAPERS
(51, 125, 136, 139, 159, 189, 245, 246, 247, 248, 249, 250, 281, 294, 295, 296, 297, 298, 299,300,301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313,314, 315,316, 317, 318, 319,320, 321, 322, 323, 324, 325,326, 327, 328, 329,330, 331, 332)

PANEL STUDIES
(158, 255, 256, 265, 333, 334, 335, 336, 337, 338, 339, 340,341, 342,343)

RESPIRATORY ADMISSIONS PAPERS
(157, 159, 251, 294, 296, 309, 331, 344, 345,346, 347, 348,349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359,360,361, 362, 363, 364, 365, 366,367, 368, 369,370)

Table 3: Summary of studies measuring short-term effect on lung function.

Outcome	Subjects	Age	Nº studies with change in lung function	
			Negative	Positive
PEFR	Symptomatic	Child	3 (2*)	0
	Healthy	Child	10 (2*)	2 (1*)
		Adult	2 (1*)	0
FEV1	Healthy	Child	10 (6*)	0
		Adult	2 (2*)	0

*: number of single studies with a p-value < 0.05

References
(158, 253, 255, 257, 265, 333, 334, 335, 336, 337, 338, 339, 340, 341, 343, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383)

Table 4: Short-term effects of ozone on lung function, biological and other responses

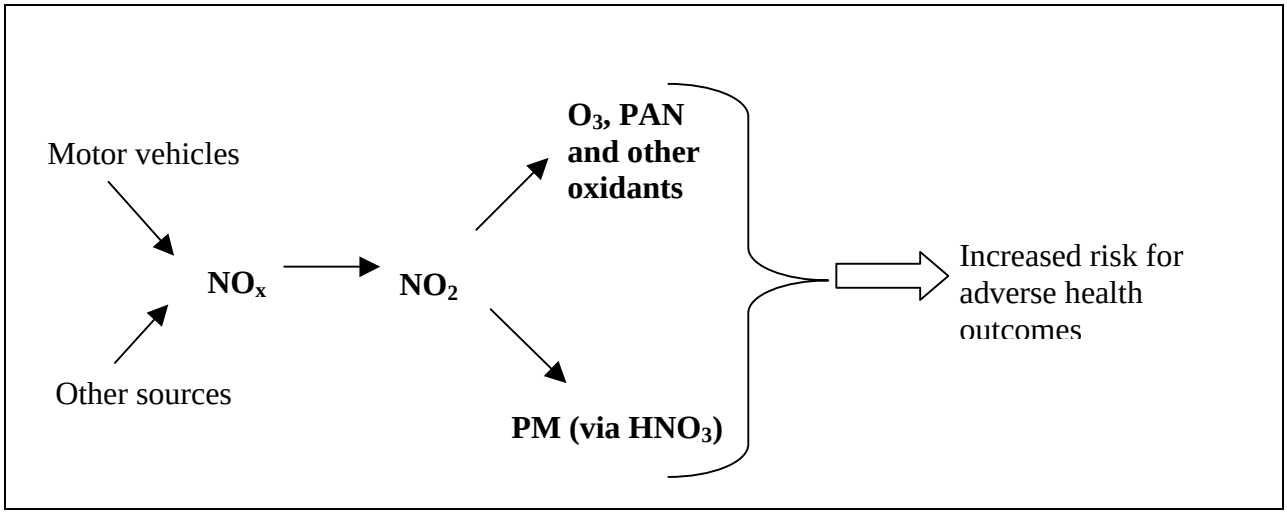
Reference	Population	Exposure	Results
Broeckaert et al 2000 (222)	Cyclists	In quartiles mean 48,72, 89 and 96 ppb	Significant elevations in CC-16 protein measured in Clara cells for those exposed to 3rd and 4th quartile
Holz et al 2002 (224)	Allergic asthmatics		**ENHANCED FUNCTIONAL AND INFLAMMATORY BRONCHIAL RESPONSE TO INHALED ALLERGEN CHALLENGE**
Frampton et al 1995 (214)	Healthy and allergic asthmatic nonsmokers	3 hours to 80, 120 and 160 ppb after exposure to H_2SO_4 and NaCl	Small, significant reductions in FVC, FEV in the highest exposure group, greater for those exposed to H_2SO_4 and bigger for asthmatics
Frank et al 2001 (223)	Young adults	0.25 ppm for 2h over 4 days	Spirometric values show adaptation, persistent small airway dysfunction/resistance
Devlin et al 1997 (215)	Young male adults	Repetitive exposures 0.4ppm for 2h over 5 days	Inflammatory mediators are attenuated, some do not return to normal after 20 days upon O_3 challenge. Several markers of cell injury are not attenuated

7 Nitrogen dioxide (NO_2)

7.1 Introduction

As for PM and O_3, the evidence on NO_2 and health comes from different sources of information, including observational epidemiology, controlled human exposures to pollutants and animal toxicology. The observational data are derived from studies outdoors where NO_2 is one component of the complex mixture of different pollutants found in ambient air and from studies of NO_2 exposure indoors where its sources include unvented combustion appliances. Interpretation of evidence on NO_2 exposures outdoors is complicated by the fact that in most urban locations, the nitrogen oxides that yield NO_2 are emitted primarily by motor vehicles, making it a strong indicator of vehicle emissions (including other unmeasured pollutants emitted by these sources). NO_2 (and other nitrogen oxides) is also a precursor for a number of harmful secondary air pollutants, including nitric acid, the nitrate part of secondary inorganic aerosols and photo oxidants (including ozone). The situation is also complicated by the fact that photochemical reactions take some time (depending on the composition of the atmosphere and meteorological parameters) and air can travel some distance before secondary pollutants are generated.
These relationships are shown schematically in Figure 1.

Figure 1: Simplified relationship of nitrogen oxides emissions with formation of NO_2 and other harmful reaction products including O_3 and PM



Health risks from nitrogen oxides may potentially result from NO_2 itself or its reaction products including O_3 and secondary particles. Epidemiological studies of NO_2 exposures from outdoor air are limited in being able to separate these effects. Additionally, NO_2 concentrations closely follow vehicle emissions in many situations so that NO_2 levels are generally a reasonable marker of exposure to traffic related emissions.

Given these complex relationships, findings of multivariate models that include NO_2 and other pollutants need cautious interpretation. While multi-pollutant models have been routinely applied to various forms of observational data, they may mis-specify underlying relationships. Even models that include only NO_2 and PM, NO_2 and O_3, or NO_2, PM and O_3 do not reflect the interrelationships among these pollutants. Statistical models considering interactions must be

based on a strong a priori hypothesis about the nature of these interactions to allow their interpretation. With these constraints in mind, the working group recommended against using regression coefficients for NO_2 from regression models for the purpose of quantitative risk assessment.

Evidence of the health effects of NO_2 by itself thus comes largely from toxicological studies and from observational studies on NO_2 exposure indoors. The studies of outdoor NO_2 may be most useful under the following circumstances:

- Evidence for NO_2 effects assessed at fixed levels of exposure to other pollutants
- Evidence for modification of the effect of PM by NO_2, possibly indicating a potential consequence of HNO_3 vapour and/or PM nitrate.

7.2 Answers and rationale

1) Is there new scientific evidence to justify reconsideration of the current WHO Guidelines for nitrogen dioxide (NO_2)?

Answer:

The current WHO guideline values for NO_2 are a 1-hour level of 200 µg/m^3 and an annual average of 40 µg/m^3. Since the previous review, only a small number of additional human exposure studies have been carried out. These do not support the need to change the 1-hour guideline value. With regard to the annual average, there have been some new epidemiological studies reporting associations of longer-term exposure with lung function and respiratory symptoms. The former group that proposed the annual guideline value of 40 µg/m^3 acknowledged that "although there is no particular set of studies that clearly support the selection of a specific numerical value for an annual average guideline the database nevertheless indicates a need to protect the public from chronic nitrogen dioxide exposures". Because of a lack of evidence, the former group selected a value from a prior WHO review. The new evidence does not provide sufficient information to justify a change in the guideline value. Given the role of NO_2 as a precursor of other pollutants and as a marker of traffic related pollution, there should be public health benefits from meeting the current guidelines. Thus the present working group did not find sufficient evidence to reconsider the current 1-hour and annual WHO guidelines for NO_2.

Rationale:

Ambient air NO_2 is in large part derived from the oxidation of NO, the major source of which is combustion emissions, mainly from vehicles. NO_2 is therefore a clear indicator for road traffic. NO_2 is also subject to extensive further atmospheric transformations that lead to the formation of O_3 and other strong oxidants that participate in the conversion of NO_2 to nitric acid and SO_2 to sulphuric acid and subsequent conversions to their ammonium neutralization salts. Thus, through the photochemical reaction sequence initiated by solar-radiation-induced activation of NO_2, the newly generated pollutants formed are an important source of nitrate, sulphate and organic aerosols that can contribute significantly to total PM_{10} or $PM_{2.5}$ mass. For these reasons, NO_2 is a key precursor for a range of secondary pollutants whose effects on human health are well documented.

Short-term chamber studies with humans (384, 385) as well as in animal exposure studies continue to support the view that at the levels encountered in the ambient outdoor air, direct effects of NO_2 alone on the lungs (or any other system) are minimal or undetectable. At NO_2 concentrations in excess of those achieved in outdoor air (with the possible exception of road tunnels), mild airway inflammation occurs (386). Human chamber studies have shown that in allergic subjects NO_2 can enhance the effect of allergens (387, 388, 389). Bronchial reactivity also was increased in the presence of NO_2 (390). These studies show effects at levels twice or more of the current guideline value and therefore do not provide evidence to justify a change.

The number of time-series studies using peak hourly concentrations and/or daily mean concentrations of NO_2 as air pollution indicators has grown substantially over the past five years. Overall, these studies have supported associations between ambient NO_2 concentrations and a range of adverse health effects. A meta-analysis on mortality showed consistent associations with NO_2 (391). Hospital admissions for respiratory disease were shown to increase with increasing levels of NO_2 in some areas (357). While such studies have supported an association between ambient NO_2 concentrations in relation to multiple respiratory and cardiovascular health outcome measures, these cannot establish causality for an NO_2 effect. It is likely that many health effects observed occur as a result of exposure to confounding traffic related pollutants and/or secondary pollutants that include O_3, acid aerosol and particles. In a significant proportion of the epidemiological studies increased risks of adverse health outcomes diminish considerably or become non-significant when other pollutants are considered in the statistical models. In others, however, NO_2 enhances the magnitude of effects observed with other pollutants (29, 349).

Recent epidemiological studies have shown consistent associations between long term exposure to NO_2 and lung function in children (22, 23, 236) as well as with lung function and respiratory symptoms in adults. These effects cannot be attributed to NO_2 exposure per se. Few studies have attempted (or had the data) to evaluate the relative contribution of particulate matter and NO_2 on the health outcomes described. Those who were able to do this show a separate but smaller contribution of NO_2 (392).

The importance of NO_2 as a key component for the rise of secondary toxic pollutant concentrations in ambient air and its potential in mixtures to enhance the effects of other environmental pollutants including allergens, warrants a guideline that limits the resulting health effects. Indeed, some additional emphasis might be given to NO_2 for the very reason that it is a good indicator of traffic-related air pollution and an important source of a range of more toxic pollutants that probably act in combination to produce adverse health effects.

2) Which effects can be expected of long-term exposure to levels of NO_2 observed currently in Europe (both pre-clinical and clinical effects)?

Answer:

The epidemiological studies provide some evidence that long-term NO_2 exposure may decrease lung function and increase the risk of respiratory symptoms.

Rationale:

Although there are fewer epidemiological studies on long-term respiratory effects of NO_2 than those of particulate matter, new evidence has been provided in recent years. Both cross-sectional and longitudinal studies indicate an association between NO_2 and lung function. The Southern California Children's Study showed that lung function levels among 9 to 16 year old children were lower in communities with higher NO_2 concentration (236). Lung function growth, evaluated in a longitudinal study, was also impaired among these children (22, 23). The NO_2 effect in the cohort study was robust when other pollutants (e.g. PM_{10} and O_3) were included in the statistical model, but weakened when acid vapours (including NO_2 derived nitric acid) were simultaneously considered. The cross-sectional SAPALDIA Study in Switzerland (93, 392) gives support to the association of NO_2 exposure and lung function decrements among adults.

Two cross-sectional studies among children (79, 393) provide some evidence of an association between NO_2 and acute bronchitis, while the Southern California Children's Study suggested that chronic respiratory symptoms (cough and phlegm) were more frequent among children with asthma in communities with higher NO_2 exposure (88). Two cross-sectional studies found an association between NO_2 and cough and phlegm symptoms in adults (94, 394).

In most of these studies, NO_2 concentrations at the community level were correlated with PM and ozone, making it difficult to disentangle an effect of NO_2 per se. In the SAPALDIA study (392), however, there was a clear association of personal exposure to NO_2 with lung function (FVC and FEV_1) within the same communities of presumably rather homogeneous PM concentrations.

3) Is there a threshold below which no effects of NO_2 on health is expected to occur in all people?

Answer:

The evidence is not adequate to establish a threshold for either short or long-term exposure. While a number of epidemiological studies have described concentration-response relationships between ambient NO_2 and a range of health outcomes, there is no evidence for a threshold for NO_2.

Rationale:

As noted in the introduction, threshold points in dose-response relationships are not readily established, based on either experimental or observational data. For the acute effects of NO_2, the evidence comes primarily from human exposure studies at concentrations in the range of several hundred $\mu g/m^3$ and higher. In general, current exposures in Europe are below this range. Thus, human exposure studies carried out with relatively small numbers of health volunteers do not provide any evidence for the existence of thresholds in a range relevant to current standard setting.

For the effects of chronic exposure, the detection of possible thresholds is complicated by the relationship between NO_2 and the formation of O_3 and of secondary particulate matter. For these secondary pollutants, thresholds have not been demonstrated and adverse effects are observed at currently prevalent levels, even towards the lower end of the concentration range. For NO_2 itself, the relevant evidence comes primarily from a few selected studies of outdoor air pollution and also from the studies of indoor air pollution (395). Although the evidence needs to be interpreted

with the above limitations in mind, several studies show associations of NO_2 with adverse health outcomes at current levels of exposure without strong evidence for a threshold. In a meta-analysis of time-series studies carried out recently (391), the overall effect estimate for NO_2 and all-cause mortality was positive. The SAPALDIA Study found evidence of adverse respiratory effects in adults in Switzerland in both cross-sectional and longitudinal data (94, 392, 396). The effects of NO_2 occurred at a mean concentration in the range of 30 $\mu g/m^3$. The authors noted the difficulty of separating the effects of NO_2 from the effects of other pollutants. The indoor studies provide mixed evidence for effect of NO_2 and are inadequate for the purpose of determining a threshold for adverse effects.

4) Are effects of NO_2 dependent upon the subjects' characteristics such as age, gender, underlying disease, smoking status, atopy, education, etc.? What are the critical characteristics?

Answer:

In general, individuals with asthma are expected to be more responsive to short-term exposure to inhaled agents, when compared to individuals without asthma. Controlled human exposure studies of short-term responses of persons with and without asthma to NO_2 have not been carried out. There is limited evidence from epidemiological studies that individuals with asthma show steeper concentration-response relationships. Small-scale human exposure studies have not shown consistent effects of NO_2 exposure on airways reactivity in persons with asthma, even at exposure levels higher than typical ambient concentrations. As for other pollutants, children can reasonably be considered to be at increased risk. There is limited evidence for influence of the other listed factors on the effects of NO_2.

Rationale:

In healthy adults changes in lung function in experiments with controlled human exposure to NO_2 occur only at concentrations in excess of those normally encountered in ambient air. However, asthmatic subjects are characterized by having airways that are hyper-responsive to a wide variety of inhalation stimuli and, as a consequence, might be expected to exhibit a greater airways response to NO_2 than in normal subjects. Small scale human exposure studies in adult asthmatics with mild to moderate disease have failed to demonstrate consistent effects of NO_2 on either baseline airway calibre or on direct (e.g., methacholine) or indirect (e.g., SO_2, cold air) airway hyper-reactivity even at concentrations higher than those typically achieved in outside air (397, 398, 399, 400). It is noteworthy that there are no studies that have included both normal and asthmatic subjects in the same study, nor patients with severe disease.

Some cross sectional studies in adults and children have shown associations between ambient NO_2 concentrations and impaired lung function (93, 236, 392, 401, 402) but it is not possible to determine whether this is due to NO_2 itself or to the secondary pollutants that are derived from it. Several new longitudinal cohort studies have also shown associations between outdoor NO_2 concentrations and impaired growth in lung function (22, 23, 24, 235) but this effect is mostly weakened when the pollutant models take account of the effects of other outdoor pollutants such as ozone, particles or acid aerosols and indoor exposures. In the study of Horak et al. (235)), a seasonal difference was found with NO_2 enhancing the effect of PM_{10} on lung function in the summer and vice versa in the winter.

Cross sectional studies using symptoms, lung function and hospital admissions have provided some evidence for an increased association between NO_2 exposure and asthma but the effects are not consistent (79, 94, 231, 233, 236, 393, 394, 402, 403, 404, 405). As with the cross section and cohort studies, NO_2 effects on asthma appear to be more prominent in children (231, 233, 236, 393, 402, 403, 405) than in adults (94, 394, 403) as observed for the aggravating effects of other air pollutants on asthma (79). As might be predicted, there are also greater associations between outdoor NO_2 exposure and respiratory outcome measures in children who spend more time outdoors (22, 24). Some epidemiological studies have reported gender effects of NO_2 on asthma or lung function changes but these are inconsistent.

There is also limited evidence that lower educational attainment is a risk factor for NO_2 with risk estimates that are independent of smoking, diet or alcohol, but less than observed for particulate matter and could be explained by increased exposure to air pollutants (12, 13, 392).

5) To what extent is mortality being accelerated by long and short-term exposure to the pollutant (harvesting)?

Answer

Methodological limitations constrain identification of harvesting due to NO_2 itself. The few long-term studies have not shown evidence for association between NO_2 and mortality. Associations have been observed between NO_2 and mortality in daily time-series studies, but on the basis of present evidence these cannot be attributed to NO_2 itself with reasonable certainty.

Rationale:
The number of cohort studies investigating associations of long-term exposure to NO_2 in ambient air with mortality is small. Neither the Six Cities Study with data from a cohort of 8 111 individuals followed over 15 years (82) nor the American Cancer Study with data from 500 000 individuals followed over 15 years (13) nor the ASHMOG study with 6 338 non-smoking Adventists in California (9) found an association of mortality risks with outdoor measured NO_2. A recent publication from the Netherlands Lung Cancer Study with a sample of 5 000 people followed over 8 years investigated mortality associations with long-term exposure to black smoke and nitrogen dioxide concentrations at the subjects' home addresses. Cardiopulmonary mortality was associated with background concentration of both pollutants but more consistently with living near a major road (12). These results point to the importance of road traffic exhaust, for which NO_2 may be an indicator.

A Czech case-control study on air pollution and infant respiratory mortality showed associations with TSP and NO_x (75). The findings are possibly mediated by a higher susceptibility for infections in more polluted air as observed in time-series studies with hospital admissions and mortality data of infants and cannot be attributed to NO_x alone.

Many recent publications on time-series studies report associations between one hour or 24-hour average concentrations of outdoor NO_2 and mortality modelling ambient NO_2 in single pollutants models. The NMMAPS Study with data for NO_2 from 19 cities in the United States of America did not find such an association (27). The European study on short-term exposure to air pollution and mortality and morbidity, APHEA, investigated data from 29 cities and found heterogeneity between the cities. In addition, higher signals for PM_{10} were detected in cities with higher mean

NO_2 levels (29). The reason for this finding is currently unclear. It could, for example, be due to interactions in atmospheric chemistry or at the pathophysiological level.

A Canadian research team published meta analyses on several gaseous pollutants and particles with mortality data from 109 studies published between 1982 and 2000 summing up 32 different estimates for NO_2 from single pollutant models. They found an overall effect estimate for NO_2 of similar magnitude as for PM_{10}, ozone or carbon monoxide (391). A larger effect size was observed for respiratory mortality. In the multi-pollutant model the effect size for total mortality dropped to one third and became non-significant, supporting the view that the concentration-response signal generated for NO_2 may largely be the consequence of exposure to other pollutants related to NO_2.

6) Is the considered pollutant per se responsible for effects on health?

Answer:

The evidence for acute effects of NO_2 comes from controlled human exposure studies to NO_2 alone. For the effects observed in epidemiological studies, a clear answer to the question cannot be given. Effects estimated for NO_2 exposure in epidemiological studies may reflect other traffic related pollutants, for which NO_2 is a surrogate. Additionally there are complex interrelationships among the concentrations of NO_2, PM and O_3 in ambient air.

Rationale:
Controlled human exposure studies have been used to investigate the effects of NO_2 *per se* and were used as the basis for establishing the current 1-hour guideline value.

In epidemiological studies, NO_2 concentrations are often highly correlated with levels of other ambient pollutants either being emitted by the same sources or related through complex atmospheric reactions. NO_2 has been found to be an indicator for (often unmeasured) traffic related pollutants such as organic and elemental carbon or freshly emitted primary ultrafine particles. This view is supported by analyses of sources of PM including gaseous pollutants where NO_2 is found to correlate well with traffic (406). In addition, NO_2 might be a marker for the contribution of NO_x to the formation of secondary pollutants such as secondary particles and O_3.

It is important to note that measurement errors with regard to population average exposure will be important when comparing effects of different pollutants. In time-series analyses, pollutants with homogenous within-city distributions will be inherently favoured over pollutants with an inhomogeneous distribution. Thus while fine particulates may have a relatively homogenous distribution over wider distances, NO_2, NO, CO and ultrafine particulates may be strongly "disadvantaged" as exposure variables in time-series analyses due to their much lager spatial variability (145). As already stated in response to question 5, a meta analysis of time-series investigations on mortality which included 109 studies published between 1982 and 2000 was conducted by Stieb et al (391). This analysis included 32 effect estimates for NO_2 from single-pollutant models and 15 from multi-pollutant models. Over a range of 24-hours average NO_2 concentration from 20 to 103 $\mu g/m^3$, the overall effect estimate from the single pollutant model for all-cause mortality was $2.8 \pm 0.3\%$ (mean $\pm$ SEM) per 44 $\mu g\ NO_2/m^3$, which fell to $0.9 \pm 0.5\%$ in multi-pollutant models. The multi-pollutant models included particle measures and sometimes

in addition O_3 or other gaseous pollutants, further supporting the view that the concentration response signal generated for NO_2 is largely, but not necessarily entirely, the consequence of other pollutants emitted by the same source or being derived from NO_2.

In long-term studies, the spatial inhomogeneity of NO_2 levels within a city might weaken the ability to detect effects of NO_2 based on measurements from urban background sites such as in the Harvard Six City Study or the American Cancer Society Study. However, NO_2 has been shown to be an appropriate indicator for assessing long-term exposure to traffic related air pollution. An example of a long-term study using this inhomogeneity is a recent European cohort study on mortality (12). The within-community variability was also used in the SAPALDIA Study (392) to capture the effects of NO_2 pollution beyond the variability that would exist for PM alone. However, associations found between ambient NO_2 concentration and health outcomes could also be explained by exposure to road traffic exhaust (79, 394, 407) and/or when it was available by exposure to particulate matter (79, 93, 94).

Therefore, the interpretation of the short-term as well as long-term epidemiological studies is that these results are not primarily due to NO_2 per se but to other unmeasured traffic related pollutants or to secondary pollutants, which have complex interrelationships with NO_2. Potential pollutants for which NO_2 might be an indicator include black smoke, organic and elemental carbon and ultrafine particles (see also section on PM).

7) For PM: which of the physical and chemical characteristics of particulate air pollution are responsible for health effects?

Not relevant for nitrogen dioxide.

8) What is the evidence of synergy / interaction of the pollutant with other air pollutants?

Answer:

There have been few controlled human exposure studies on interactions with other chemical pollutants, although several studies show that NO_2 exposure enhances responses to inhaled pollens. Some epidemiological studies have explored statistical interactions of NO_2 with other pollutants, including particles, but the findings are not readily interpretable.

Rationale:

The number of new studies using human controlled exposures to assess the effect of multiple pollutants including NO_2 is limited. The combination of NO_2 and O_3 was addressed by (408) showing a reduction in cardiac output which was largest for NO_2 in combination with O_3. Human controlled exposure studies have suggested that single and multiple controlled exposures to concentrations of NO_2 in excess of those normally achieved in ambient air can sensitize the airways of adult asthmatic subjects to the bronchoconstrictor effect of an inhaled allergen to which they are specifically sensitized (387, 388, 389, 409, 410, 411). The late response defined as 3 to 10 hours after administration of sub-acute allergen concentrations seemed to be more affected than the immediate response. Short term exposure to air pollutants (including NO_2) in a road tunnel has also been shown to enhance the asthmatic response to allergen (207). The

mechanistic basis for these interactions has not been elucidated. The studies might suggest that NO_2 can exhibit a “priming” effect, by for example affecting epithelial function.

Epidemiological time-series analyses addressing possible synergisms between NO_2 and other pollutants have focused on the role of NO_2 as an effect modifier of the association between PM and health outcomes. In the APHEA2 study, PM associations with daily mortality were larger in areas with high NO_2 concentrations (29). In contrast in the NMMAPS study, no evidence for effect modification of the association between PM and daily mortality by NO_2 was found (27). A possible interpretation of the APHEA2 results could be that NO_2 might serve as an indicator for the presence of more toxic particles such as traffic related particles. In the light of the NMMAPS results however, the assumption needs to be made that in European cities NO_2 is a better traffic indicator than in North American cities. Generally, the statistical analyses assessing effect modification carry with them the inherent limitation that in complex mixtures the pollutants themselves are indicators and that measurement error further reduces the ability to disentangle their contributions as discussed in the rationale on question 6. With the level of evidence available it is not yet possible to state with a sufficient degree of confidence whether NO_2 is able to synergize with PM or to state that NO_2 is a valid indicator for more toxic PM present under these conditions.

9) What is the relationship between ambient levels and personal exposure to the pollutant over short-term and long-term (including exposures indoors)? Can the differences influence the result of studies?

Answer:

In any particular setting the answer will depend on the relative contributions of outdoor and indoor sources and on personal activity patterns. A direct relationship between personal exposure and outdoor concentrations is found in the absence of exposure to indoor sources such as unvented cooking or heating appliances using gas, and tobacco smoking. However, since outdoor NO_2 is subject to wide variations caused by differences in proximity to road traffic and local weather conditions, the relationship of personal exposure to measurements made at outdoor monitoring stations is variable. Results of epidemiological studies relying on outdoor NO_2 concentrations may be difficult to interpret if account is not taken of exposure to indoor sources.

Rationale:

An individual’s exposure to NO_2 from outdoor sources will depend largely on their proximity to vehicular traffic in space and time, given that mobile sources are the chief contributors to ambient NO_2 in contemporary European cities (see Question 10). Ambient NO_2 concentrations measured at fixed urban sites may not accurately reflect personal exposure to NO_2 from outdoor sources, because ambient NO_2 concentrations vary widely in most locales due to traffic patterns, the characteristics of the built environment, and meteorologic conditions (412). Fixed monitors are not necessarily sited with the intent of reflecting the population average exposure, and, therefore, the accuracy with which their measurements reflect population exposures may vary. This may be particularly pronounced with regard to short-term exposure in the order of days (128).

NO_2 measurements from fixed-site monitors may provide better indices of exposure over longer time periods depending on where the monitors are located. For example, good relationships

between personal and ambient NO_2 concentrations have been observed in areas with high traffic densities (412). Such measurements, including concentrations measured at fixed residential locations ("front door" concentrations) may be particularly useful indicators of exposure to traffic-related pollution, especially when combined with data on individual time-activity patterns, traffic patterns, and other geographical information (19).

NO_2 from indoor sources, e.g., gas cooking and heating, and ETS, contributes importantly to individual exposure when such sources are present, and may reduce the relationship between individual exposure and ambient concentrations measured at outdoor fixed sites (413, 414, 415). Epidemiological studies of the effects of long-term exposure to NO_2 from outdoor sources need to take the possible correlation between indoor and outdoor concentrations into account in order to ensure that their effects are not confused. Fortunately, there is less need for such concern in studies of the acute effects of short-term exposure (e.g., daily time-series studies of mortality) because there is little reason to expect that concentrations of NO_2 from indoor and outdoor sources would be correlated over such short-time intervals.

10) Which are the critical sources of the pollutant responsible for health effects?

Answer:

In most urban environments in Europe, the principal source of NO_2 is NO_x from motor vehicles of all types and energy production in some places.

Rationale:
Nitrogen dioxide is formed in the environment from primary emissions of oxides of nitrogen. Although there are natural sources of NO_x (e.g., forest fires), the combustion of (fossil) fuels has been, and remains, the major contributor in European urban areas. Over the past 50 years vehicular traffic has largely replaced other sources (e.g., domestic heating, local industry) as the major outdoor source of NO_x from fossil fuel combustion, and hence NO_2: earlier in western Europe, more recently in eastern Europe. Other, stationary, sources (e.g., power plants or domestic) also contribute to NO_x emissions, and, therefore to outdoor concentrations of NO_2 in certain areas.

In the European Union vehicular traffic contributes more than half of the emissions of NO_x (416). This is more than in the United States of America, but the contribution to total NO_x emissions is even higher in some European cities, based on data from the 1990s. In London, for example, road transport contributes 75% of NO_x emissions (417). Due to their characteristics (low emission heights; high emission densities in urbanized areas), traffic emissions are often the dominating source of urban outdoor NO_2 exposure.

11) Have positive impacts on public health of reduction of emissions and/or ambient concentrations of NO_2 been shown?

Answer:

No recent peer reviewed publication could be found to answer this question.

Rationale:
It has not been possible to study impacts of reduction in NO_x emissions or NO_2 concentrations in the ambient air because there have been no good examples of such reductions. In Europe, there have been moderate decreases in emissions (416) and ambient concentrations in urban areas (418) in the last decade. In the United States of America, reduced emission rates from individual vehicles and power plants have been offset by increases in vehicle km travelled from road transport, leaving ambient levels relatively constant over the past decades.

12) What averaging period (time pattern) is the most relevant from the point of view of public health and would additional protection be provided by setting standards for more than one averaging period for NO_2?

Answer:

With regard to protection against acute health effects, either the peak-hour average or 24hr (daily) average NO_2 concentrations can be used as a measure of direct short-term exposure, since they are highly correlated in urban areas. Having a longer-term guideline value is also supported by the evidence on possible direct effects of NO_2, and on its indirect consequences through the formation of secondary pollutants.

Rationale:
The limited data on short-term responses to controlled NO_2 exposures in chamber studies does not provide any guidance on the relevant averaging time for the physiological responses on the scale of hours to days. However, this is a less important issue in terms of a guideline because of the high correlation of hourly maximum with daily average values.

In terms of the long-term effects of NO_2 and/or the secondary pollutants that result from the presence of NO_2 in the ambient air, maintaining an annual NO_2 WHO guideline value is most appropriate. Effective implementation of an annual NO_2 guideline, especially at or near the current level, would necessitate reductions in ambient NO_2 concentrations in highly populated regions in Europe. Such reductions in NO_2 can be expected to reduce the secondary pollutant concentrations as well.

8 Recommendations: follow up actions

The ultimate goal of any clean air policy is to develop strategies to reduce the risk of adverse effects on human health and the environment as a whole caused by ambient air pollution. With the existence of very susceptible populations and the ability to detect effects even if they are infrequent, we may be confronted with situations when the concept of thresholds is no longer useful in setting standards to protect public health. The principle of eliminating adverse effects with an adequate margin of safety even for the most susceptible groups may not be realistic. However, risk reduction strategies are and will continue to be powerful tools in promoting public health. The development of such strategies requires not only qualitative, but also quantitative knowledge on the most relevant adverse effects.

Therefore, the working group recommended, as a follow up of this work, a meta-analysis using the bibliographic database developed at the St George's Hospital Medical School. This meta-

analysis should be guided by a small task group and should derive updated cause-specific risk coefficients for the following health endpoints, which can also be used in subsequent health impact assessments:
Ozone

- Mortality short-term: all causes all ages
- Respiratory hospital admissions: adults, children, elderly
- Symptom exacerbation in asthmatics

PM ($PM_{2.5}$; coarse; BS; PM_{10})

- Mortality short-term
- Hospital admissions/Emergency room visits

The working group also recommended

- an update of the concentration-response table for O_3 in the current WHO AQG, which is based on controlled exposure, considering lung function and inflammation under new evidence and
- an identification of those risk coefficients to be used within CAFÉ to estimate long term mortality in relation to PM exposure.

In addition, the working group noted that the recommendation to use $PM_{2.5}$ as indicator for PM-related health effects does not imply that $PM_{2.5}$ is the only relevant parameter to characterize PM pollution. Therefore, it was recommended to set up a more comprehensive monitoring programme in different European cities (possibly including PM_{10}, $PM_{2.5}$, PM_1, BS, PM composition, gases), which, in combination with properly designed health studies, could lead to an additional gain in knowledge on the health effects of ambient air pollution in the coming years.

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Annex 1

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Annex 2

USE OF BIBLIOGRAPHIC DATABASE FOR SYSTEMATIC REVIEW

By Richard Atkinson, St George's Hospital Medical School, London, United Kingdom

METHOD

1. Identification of time series and panel studies

Three bibliographic databases were searched: Medline, Embase and Web of Science. Separate search strings for each study type, time series and panel, were used. These were tested against known literature until we were satisfied that the search strings were sensitive enough to pick up all relevant studies. The full reference and abstract for each of the citations identified by the searches were downloaded from the source bibliographic databases into Reference Manager (RM) databases, one for potential time series studies and one for potential panel studies. Within each of the RM databases the studies were assigned unique identification codes.

Papers already available to the academic department were checked for inclusion in the RM databases. Citations in reviews of the published literature (such as the recent consultation document on particles published by the United States Environmental Protection Agency) were also checked to ensure that no relevant papers were missed.

The process of identifying time series or panel studies from those selected by the search strings comprised two stages. First, the abstracts of all studies were reviewed and obvious non-time series and non-panel studies (e.g. clinical, mechanistic, exposure assessment) were removed from the RM databases. In the second stage, copies of the remaining studies were obtained and the time series and panel studies identified.

Once the time series and panel studies had been identified they were assigned a code within RM indicating whether or not they provided *usable* numerical estimates of the effects of air pollution. If they did not provide usable estimates then the reason(s) was also recorded. Studies were classified as follows:

- studies providing *usable* numerical estimates of the effects of air pollution;
- studies providing numerical estimates that were *unusable* (e.g. because of inappropriate statistical methods or insufficient data provided in the paper);
- studies which did not provide numerical estimates for the effects of air pollution (e.g. where the association between air pollution and health is assessed using a correlation coefficient);
- those studies which reviewed published literature;
- those studies using existing data or simulated data to develop new analytical techniques;
- others (letters, editorials, errata, meeting abstracts, case crossover and case control study designs).

2. Studies providing usable numerical estimates

For all time series and panel studies providing usable regression estimates a number of items of data were identified, recorded on a coding sheet and then entered into Access databases, one containing details of results for all time series studies and the other containing similar information for all panel studies. These data described basic features of each study as well as recording the regression coefficients, standard errors and the information necessary to calculate standardized estimates of the health effects of each pollutant. We also included variables that described relevant elements of the analysis such as the length of the study period, year of study, continent, average pollution levels etc. General information about each study contained in the RM databases (title, authors, journal reference etc.) was also downloaded into the Access databases. These study specific data were linked to the result specific data using the relational features of the Access software.

3. Studies providing unusable numerical estimates

A number of studies contained numerical estimates but were not included in the Access databases. The reason(s) for their exclusion were coded in the RM databases and fell largely into two categories, statistical method and data quality. The former included studies that did not control for seasonality and other confounders adequately and the latter included studies that were of a very limited period or a very small population (e.g. a single hospital).

4. Presentation of results

In time series studies, relative risks, regression estimates and percentage changes in the mean number of events per day were all used to assess the association between the pollutants and health outcomes. In order to make results comparable estimates from Poisson and log-linear models (relative risks, regression estimates and percentage changes) were converted into a standard metric: percentage change in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in the pollutant (100 mg/m^3 increase for CO). Access queries were written to calculate these adjusted estimates. Estimates from linear models were standardized to the change in the number of events associated with 10 $\mu g/m^3$ increases in the pollutant (100 mg/m^3 increases for CO). Where the logarithm of the pollutant was used in the model, the results were quoted for a unit change in the pollutant level on the logarithmic scale – in other words, the number of health events or percentage change in the number of health events associated with a doubling of the pollutant level.

A similar process was undertaken for panel study results. Most studies using binary outcomes used logistic regression and presented odds ratios. These have been converted to represent 10 $\mu g/m^3$ increases in the pollutant. The results for continuous outcomes were usually given as betas, sometimes as percentage change. These have been converted to betas for 10 $\mu g/m^3$ increases in the pollutant. Results recorded as percentage change have been converted to betas where this was possible (only a few cases). Units for lung function were standardized to litres (L) or L/min as appropriate.

Access forms provide a user interface to the databases. They allow the user to select a set of the results defined by the outcome, disease, age group, pollutant etc. The standardized regression estimates are calculated and then displayed using a “forest” plot. The estimates are assumed to come from Poisson or log-linear models with linear terms for the pollutants. Results from other model specifications or where a non-linear term for the pollutant was used are highlighted on the plot.

5. Selection of lags

Many studies investigated and reported results for a number of pollutant lags or days prior to the health events. Some studies specified an *a priori* lag for investigation whilst others investigated a number of lags and reported only those that had the largest (or largest positive) effect or were statistically significant. It was desirable to be able to specify the lag for specific analyses but also it was essential that a result for each outcome/pollutant combination from each study could be easily selected for presentation without reference to a specified lag. For a given outcome defined by event type (mortality/admission etc.), disease group and age group and a given pollutant, a single result was extracted and denoted as the "selected" result for that combination of outcome and pollutant. The selection was made in priority order as follows:

1. Only one lag measure presented (this may be because only one was examined or only one was presented in the paper)
2. Results for more than one lag presented. The lag selected was chosen as:
   2.1 Lag focused on by author OR
   2.2 Most statistically significant OR
   2.3 Largest estimate

In addition to this selected lag, results for lag 0 and lag 1 were recorded (if different to "selected" lag from above process). A result for a cumulative lag (mean of pollution measures over 2 or more days), chosen by criteria 2.1–2.3 above was also recorded when cumulative results were available.

Some studies only provided results by season, that is, if no all-year analyses were undertaken. In these cases the selection process described above applied to each season analysed. Where only results from multi-pollutant models (two, three, four pollutants in a single statistical model) were given then the results from the model with the most pollutants in it was selected for inclusion in the Access database.

For panel studies a similar approach was used.

6. Multi-city studies

A number of recent studies have presented meta-analyses of results from several locations. As well as presenting results from each location, summary estimates have been calculated. Where such studies have used previously published data only the summary estimates have been recorded. Where previously unpublished city-specific results are presented they have been recorded separately.

7. Summary Estimates

Regression estimates and standard errors for each group of studies were transferred into STATA where standard procedures within STATA were used to calculate fixed- and random-effects summary estimates.

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