



**World Health
Organization**

REGIONAL OFFICE FOR **Europe**

Review of evidence on health aspects of air pollution – REVIHAAP Project

Technical Report



This publication arises from the project REVIHAAP and has received funding from the European Union.

ABSTRACT

This document presents answers to 24 questions relevant to reviewing European policies on air pollution and to addressing health aspects of these policies. The answers were developed by a large group of scientists engaged in the WHO project “Review of evidence on health aspects of air pollution – REVIHAAP”. The experts reviewed and discussed the newly accumulated scientific evidence on the adverse effects on health of air pollution, formulating science-based answers to the 24 questions. Extensive rationales for the answers, including the list of key references, are provided. The review concludes that a considerable amount of new scientific information on the adverse effects on health of particulate matter, ozone and nitrogen dioxide, observed at levels commonly present in Europe, has been published in recent years. This new evidence supports the scientific conclusions of the *WHO air quality guidelines*, last updated in 2005, and indicates that the effects in some cases occur at air pollution concentrations lower than those serving to establish these guidelines. It also provides scientific arguments for taking decisive actions to improve air quality and reduce the burden of disease associated with air pollution in Europe.

This publication arises from the project REVIHAAP and has been co-funded by the European Union.

Keywords

AIR POLLUTANTS
AIR POLLUTION – ADVERSE EFFECTS
ENVIRONMENT AND PUBLIC HEALTH
EVIDENCE BASED PRACTICE
GUIDELINES
HEALTH POLICY

Address requests about publications of the WHO Regional Office for Europe to:

Publications
WHO Regional Office for Europe
Scherfigsvej 8
DK-2100 Copenhagen Ø, Denmark

Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the Regional Office web site (<http://www.euro.who.int/pubrequest>).

© World Health Organization 2013

All rights reserved. The Regional Office for Europe of the World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate borderlines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not

mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use. The views expressed by authors, editors, or expert groups do not necessarily represent the decisions or the stated policy of the World Health Organization.

The views expressed herein can in no way be taken to reflect the official opinion of the European Union.

CONTENTS

Acknowledgements	v
Abbreviations.....	vi
Introduction	1
A. Health effects of PM	6
Question A1	6
Question A2	10
Question A3	32
Question A4	35
Question A5	38
Question A6	41
B. Health effects of ozone.....	47
Question B1	47
Question B2	59
Question B3	62
Question B4	64
C. Proximity to roads, NO ₂ , other air pollutants and their mixtures	67
Question C1	67
Question C2	73
Question C3	113
Question C4	117
Question C5	127
Question C6	137
Question C7	142
Question C8	155
Questions A7 & C9	165
Question C10	175
D. General questions	182
Question D1	182
Question D2	197
Question D4	208
References	215
List of invited experts participating in REVIHAAP.....	300

Acknowledgements

This publication was developed by the WHO Regional Office for Europe as part of the “Review of evidence on health aspects of air pollution – REVIHAAP” project. This project has been co-funded by the European Union under Contribution Agreement No. 07-0307/2011/604850/SUB/C3.

Abbreviations

Organizations, other entities and studies

AHSMOG	Loma Linda University Adventist Health and Smog study
AIRS	Aerometric Information Retrieval System
APED	Air Pollution Epidemiology Database
APHEA	Air Pollution and Health: a European Approach
APHEIS	Air Pollution and Health: a European Information System project
APHENA	Air pollution and health: a European and North American approach study
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry of the United States Department of Health and Human Services
BENMAP	Environmental Benefits Mapping and Analysis program
CAFE	Clean Air for Europe Programme
CLRTAP	Convention on Long-range Transboundary Air Pollution
COMEAP	the United Kingdom's Committee on the Medical Effects of Air Pollutants
CPS-II	American Cancer Society Cancer Prevention Study II
EC	European Commission
EEA	European Environment Agency
EFSA	European Food Safety Authority
EGEA	French Epidemiological study on Genetics and Environment of Asthma
EPA	United States Environmental Protection Agency
EPAQS	United Kingdom Expert Panel on Air Quality Standards
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
HEIMTSA	Health and Environment Integrated Methodology and Toolbox for Scenario Assessment project
HRAPIE	Health Risks of Air Pollution in Europe
IARC	International Agency for Research on Cancer
JECFA	Joint WHO/FAO Expert Committee on Food Additives
NAS	United States National Academy of Sciences
NHANES III	Third National Health and Nutrition Examination Survey
NMMAPS	United States National Morbidity, Mortality and Air Pollution Study
PAPA	Public Health and Air Pollution in Asia study
PEACE	Pollution Effects on Asthmatic Children in Europe project
REVIHAAP	Review of evidence on health aspects of air pollution
WHO	World Health Organization

Technical terms

CI	confidence interval
CICADs	concise international chemical assessment documents
COX-2	cyclooxygenase-2
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
HAPs	hazardous air pollutants
Hg	mercury
Hg ⁰	mercury vapour

HR	hazard ratio
ICAM-1	intercellular adhesion molecule 1
IgE	immunoglobulin E
IL-8	interleukin 8
LRTAP	long-range transboundary air pollution
LOAEL	lowest-observed-adverse-effect level
MeHg	methylmercury
MMEF	maximal mid-expiratory flow
$\mu\text{g/gC}$	micrograms per gram creatinine
NO_2	nitrogen dioxide
NOAEL	no-observed-adverse-effect level
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
PM_{10}	particulate matter with an aerodynamic diameter smaller than 10 μm
$\text{PM}_{2.5}$	particulate matter with an aerodynamic diameter smaller than 2.5 μm
$\text{PM}_{\text{coarse}}$	particulate matter with an aerodynamic diameter in the range 10–2.5 μm
PM_{fine}	particulate matter with an aerodynamic diameter smaller than 2.5 μm
ppb	parts per billion
r	Pearson correlation coefficient
Rfc	inhalation reference concentration
RR	relative risk
SO_2	sulfur dioxide
SOMO10	for ozone, the sum of means over 10 ppb (daily maximum 8-hour)
SOMO35	for ozone, the sum of means over 35 ppb (daily maximum 8-hour)
TRP	transient receptor potential

Introduction

Air pollution is an important determinant of health. A wide range of adverse effects of ambient air pollution on health has been well documented by studies conducted in various parts of the world. There is significant inequality in exposure to air pollution and related health risks: air pollution combines with other aspects of the social and physical environment to create a disproportionate disease burden in less affluent parts of society. WHO periodically reviews the accumulated scientific evidence to update its air quality guidelines. The most recent update was completed in 2005. The guidelines address all regions of the world and provide uniform targets for air quality that would protect the large majority of individuals from the adverse effects on health of air pollution.

The adverse effects on health of particulate matter (PM) are especially well documented. There is no evidence of a safe level of exposure or a threshold below which no adverse health effects occur. More than 80% of the population in the WHO European Region (including the European Union, EU) lives in cities with levels of PM exceeding WHO Air Quality Guidelines. Only a slightly decreasing trend in average concentrations has been observed in countries in the EU over the last decade. Pollution from PM creates a substantial burden of disease, reducing life expectancy by almost 9 months on average in Europe. Since even at relatively low concentrations the burden of air pollution on health is significant, effective management of air quality that aims to achieve WHO Air Quality Guidelines levels is necessary to reduce health risks to a minimum.

Exposure to air pollutants is largely beyond the control of individuals and requires action by public authorities at the national, regional and international levels. A multisectoral approach, engaging such relevant sectors as transport, housing, energy production and industry, is needed to develop and effectively implement long-term policies that reduce the risks of air pollution to health.

The EU Directive of 2008 on ambient air quality and cleaner air for Europe explicitly states that the “emissions of harmful air pollutants should be avoided, prevented or reduced and appropriate objectives set for ambient air quality taking into account relevant World Health Organization standards, guidelines and programmes”.

In that context, and in the framework of the EU’s Year of Air in 2013, the World Health Organization (WHO) Regional Office for Europe is implementing two projects: (a) evidence on health aspects of air pollution, to review EU policies – REVIHAAP; and (b) health risks of air pollution in Europe – HRAPIE”, with financial support from the European Commission (EC). These projects will provide scientific evidence-based advice on the health aspects of air pollution, to support the comprehensive review of the EU’s air quality policies scheduled for 2013. The review focuses on pollutants regulated by EU directives 2008/50/EC and 2004/107/EC.

1. Scope of the project

The advice provided by the REVIHAAP and HRAPIE projects is formulated as responses to 26 key policy-relevant questions asked by the EC. This advice is grounded in a review of the latest scientific evidence for PM, ground level ozone, nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and emissions to the air of individual metals (arsenic, cadmium, nickel, lead and

mercury) and polycyclic aromatic hydrocarbons, as regulated by EU directives 2008/50/EC and 2004/107/EC. The questions cover general aspects of importance to air quality management, as well as specific topics on health aspects of individual air pollutants. The review was conducted by invited experts from top institutions across the world. This WHO technical report from the REVIHAAP project includes answers to 24 of the questions.

Further work documents emerging issues on health risks from air pollution related to specific source categories (for example, transport, biomass combustion, the metals industry, refineries and power production), specific gaseous pollutants or specific components of PM (such as size range, like nanoparticles and ultrafine particles, and rare-earth metals, black carbon (elemental carbon and/or organic carbon)) (Question D3). Moreover, concentration–response functions to be included in cost–benefit analysis will be identified in response to Question D5. This work, under the HRAPIE project, will be concluded by September 2013, although preliminary findings will be made available to the EC earlier, to ensure their suitable use in reviewing EU air quality policies.

2. Process

A scientific advisory committee of eight scientists, experienced in previous reviews conducted by WHO and representing key areas relevant to the projects (epidemiology, toxicology and atmospheric sciences), was put together to guide and oversee the projects. Two meetings with the scientific advisory committee members were held, in December 2011 and June 2012, to provide advice and coordinate the workplan.

The review was conducted by a group of 29 invited experts from top institutions around the world, representing various relevant scientific disciplines. These experts, working in small groups, reviewed the scientific literature accumulated, drafted succinct answers to the questions and drafted longer rationales to the answer emerging from the research results. Answers to questions in section D were prepared using conclusions from answers to questions A–C.

Thirty-two invited external reviewers, as well as members of the scientific advisory committee, provided detailed comments on the completeness of the literature reviewed, the validity of conclusions reached and the clarity of the answers. The authors used the comments to revise the text, subject to further review. A full list of scientific advisory committee members, expert authors, and external reviewers is provided at the end of this document. All submitted a WHO Declaration of Interests form to ensure the review process was unbiased.

Besides discussions conducted electronically, direct discussions of the answers and evidence in their support was held at two WHO expert meetings, which took place at the WHO European Centre for Environment and Health office in Bonn, Germany, on 21–23 August 2012 and 15–17 January 2013. During the second meeting, the final text of the answers covered under the REVIHAAP project was adopted. The discussions covered solely scientific arguments, addressing the methodological quality of the influential studies, as well as the completeness and consistency of the evidence generated by studies conducted in various areas of the world, in various populations and with various scientific methods. The conclusions reflect the collective expert judgment of specialists in the field, and the final text of the answers was adopted by a consensus of experts present at the meeting.

Although some of the questions asked directly for the assessment of individual policies or policy instruments, the REVIHAP discussion and answers covered only the scientific evidence underlying the policy and did not address political arguments.

3. Sources of information and methodology

Carrying out a review of the effects on health of ambient air pollution is a challenging task, since a remarkably large body of evidence has to be assessed. Thousands of new scientific papers have been published on this topic in the last few years, covering various aspects and research disciplines, such as population exposure, observational epidemiology, controlled human exposure, animal toxicology and in vitro mechanistic studies.

With that in mind, the review of the literature in support of the answers therefore focused on studies that were published after the 2005 global update of the WHO air quality guidelines. However, when appropriate and necessary, the review also included earlier publications. Also, the group made use of recent major reviews, with a particular focus on those prepared by relevant international or national organizations. Only publications with a clearly stated methodology, for literature searches and evidence selection, were used.

A more systematic approach was used to review and assess recent individual publications. By necessity, the authors focused on the most significant and relevant studies and on meta-analyses, when available.

The evidence presented in this review is based on all available types of information, including conclusions from epidemiological and toxicological research. The main sources of evidence are quoted and the strength of this evidence is explained. Careful wording has been used throughout the document to properly present the strength of the evidence and to determine potential causality related to associations observed between air pollutants and outcomes. This wording is indicative of the state of the evidence on a particular issue.

4. Reconsideration and revision of guidelines

Several questions specifically ask whether the scientific conclusions of the 2005 global update of the WHO air quality guidelines require revision, based on the new evidence that has emerged on adverse health effects.

The group of experts thoroughly evaluated the scientific literature published since the 2005 global update of the WHO air quality guidelines and explored whether the new evidence justified reconsideration of the current guidelines. A positive answer indicates a gain in knowledge. While there are formal frameworks to assess gains in knowledge, the group relied on its collective expert judgment to determine if there was sufficient new evidence. Issues taken into consideration when interpreting the strength of the new evidence included: the identification of new adverse health outcomes; the consistency of findings of associations at exposure levels lower than previously identified; and the enhanced mechanistic understanding of the observed associations, which could lead to a reduction of uncertainty.

It is important to note that a revision of a guideline does not necessarily mean that a change in the existing WHO air quality guideline value is warranted. It rather implies that the whole body of the scientific evidence should be systematically analysed when reconsidering values that protect health. It is important to emphasize that the REVIHAAP project has not

discussed new guidelines. Based on the project's recommendations, WHO will consider initiating a separate process to update the guidelines, according to WHO rules.

5. From guidelines to limit values

Several questions ask explicitly about the impact on EU air quality legislation of the new evidence on the health effects of air pollution.

It is important to note that there is a fundamental difference between the roles and mandates of WHO and the EC. WHO holds a normative role and evaluates the scientific evidence in order to develop guidelines and recommendations, whereas the EC holds a policy role, proposing and implementing legally binding decisions within its jurisdiction.

Therefore, according to the normative role of WHO, the recommendations that stem from the REVIHAAP project are based solely on scientific conclusions on health aspects of air pollution and do not consider issues relevant to policy formulation, such as technical feasibility, economic considerations and other political and social factors.

For the protection of public health, WHO recommends maintaining levels of air pollutants below those at which adverse effects on public health have been documented. The WHO air quality guidelines are typically set at such levels. However, WHO recognizes the heterogeneity in underlying factors influencing air quality management decisions in various countries and has therefore (in the past) developed interim target values for some pollutants. These target values should promote a steady process towards meeting WHO guideline values, which are the main recommendations.

6. General issues of relevance to all pollutants

This section sets out the views of the authors on core issues embedded within some of the questions.

6.1 Pollution mixtures

The request to review the health effects of individual air pollutants separately implicitly suggests that each has adverse effects on health per se. The pollutants currently regulated in the EC directives, and covered in this document, share many common sources and are linked by complex chemical processes in the atmosphere. The group of experts recognizes that air pollution exists as a complex mixture and that the effects attributed to individual air pollutants may be influenced by the underlying toxicity of the full mixture of all air pollutants. This is also specifically addressed as part of the Answer to Question C8.

6.2 Health impact assessment

Questions A6, B3, and C4 ask what metrics, health outcomes and concentration–response functions can be used to assess the health impact of PM, ozone, and NO₂. The calculation of health impacts requires several components: (a) an estimate of current concentrations of the pollutant(s) under review; (b) a determination of the target concentration or standard, or the expected concentration change from a policy under consideration; (c) the concentration–response functions that typically relate a change in pollution to a per cent change in a health outcome; (d) a baseline level of the health outcome; and (e) a characterization of uncertainty.

Based on currently available evidence, the authors of the present review have provided recommendations in the answers to questions A6, B3 and C4, on specific pairings of pollutant exposures and specific health effects that can be used. However, further work is currently being conducted, as part of the HRAPIE project, to recommend which set of concentration–response functions could be included in the cost–benefit analysis that supports the revision of the EU air quality policy, in answer to Question D5. This work includes checking that suitable baseline rates and exposure metrics are available and discussing which health impact assessment methodologies are most appropriate in different contexts.

6.3 Critical data gaps

Questions A7 and C9 both ask about identifying critical data gaps that need to be filled, to help answer the other questions more fully in the future. These questions are restricted to section A (PM), as well as to section C (other air pollutants and their mixtures). The group of experts felt that these questions should cover all air pollutants currently regulated in EC directives. Therefore, the group decided to merge the two questions and to provide an answer that integrates all relevant critical data gaps.

A. Health effects of PM

Question A1

What new evidence on health effects has emerged since the review work done for the WHO air quality guidelines published in 2006, particularly with regard to the strength of the evidence on the health impacts associated with exposure to PM_{2.5}? Based on this new information, do the scientific conclusions given in 2005 require revision?

Answer

Since the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) were issued, many new studies from Europe and elsewhere on both short- and long-term exposure to PM with an aerodynamic diameter smaller than 2.5 µm (PM_{2.5}) have been published. These studies provide considerable support for the scientific conclusions in the 2005 global update of the WHO air quality guidelines and suggest additional health outcomes to be associated with PM_{2.5}. Among the major findings to date are the following:

1. additional support for the effects of short-term exposure to PM_{2.5} on both mortality and morbidity, based on several multicity epidemiological studies;
2. additional support for the effects of long-term exposures to PM_{2.5} on mortality and morbidity, based on several studies of long-term exposure conducted on large cohorts in Europe and North America;
3. an authoritative review of the evidence for cardiovascular effects, conducted by cardiologists, epidemiologists, toxicologists and other public health experts, concluded that long-term exposure to PM_{2.5} is a cause of both cardiovascular mortality and morbidity;
4. significantly more insight has been gained into physiological effects and plausible biological mechanisms that link short- and long-term PM_{2.5} exposure with mortality and morbidity, as observed in epidemiological, clinical and toxicological studies;
5. additional studies linking long-term exposure to PM_{2.5} to several new health outcomes, including atherosclerosis, adverse birth outcomes and childhood respiratory disease; and
6. emerging evidence that also suggests possible links between long-term PM_{2.5} exposure and neurodevelopment and cognitive function, as well as other chronic disease conditions, such as diabetes.

The scientific conclusions of the 2005 global update of the WHO air quality guidelines about the evidence for a causal link between PM_{2.5} and adverse health outcomes in human beings have been confirmed and strengthened and, thus, clearly remain valid. As the evidence base for the association between PM and short-term, as well as long-term, health effects has become much larger and broader, it is important to update the current WHO guidelines for PM. This is particularly important as recent long-term studies show associations between PM and mortality at levels well below the current annual WHO air quality guideline level for PM_{2.5}, which is 10 µg/m³. Further discussion is also provided in section D.

Rationale

The 2005 global update of the WHO air quality guideline for PM_{2.5} was based primarily on the findings of prospective cohort studies of Pope et al. (2002) on the effects of long-term exposures on mortality, with support provided by the studies of Dockery et al. (1993) and Jerrett et al. (2005). Additional scientific support for these studies was provided at the time by an independent reanalysis conducted by Krewski et al. (2000, 2004) and by a study conducted in Europe (Hoek et al., 2002b). In prospective cohort studies, a sample of individuals are selected and followed over time. For example, Dockery et al. (1993) published results for a 15-year prospective study (the Harvard Six Cities Study) based on approximately 8000 individuals in six cities in the eastern United States. Pope et al. (2002) published results of a prospective study of the mortality experience of approximately 550 000 individuals in 151 cities in the United States, using a cohort participating in a long-term investigation sponsored by the American Cancer Society. These studies used individual-level data, so that other factors that affect mortality could be characterized and adjusted in the analysis. Several different cause-specific categories of mortality were examined, including from cardiopulmonary (that is, cardiovascular plus pulmonary) and lung cancer.

Since 2005, the Harvard Six Cities Study and the study of the American Cancer Society cohort have been updated several times, with systematic increases in the number of years of analysis and deaths that were followed and in the sophistication of the statistical methodology (Laden et al., 2006; Lepeule et al., 2012; Krewski et al., 2009). These reanalyses continue to find a consistent, statistically significant association between long-term exposure to PM_{2.5} and the risk of mortality. In addition, the magnitude of the effect estimate (that is, the mortality effect per unit of exposure) remains consistent with that of the original study. Using the 51 cities from the American Cancer Society study for which long-term PM_{2.5} data are available, Pope, Ezzati & Dockery (2009) reported that metropolitan area-wide reductions in PM_{2.5} concentration between 1980 and 2000 were strongly associated with increases in life expectancy, after adjustment for changes in other risk factors. The importance of this study is that it documents that improvements in air quality are reflected in improvements in public health. The authors found results remarkably similar to the earlier American Cancer Society studies, though the methodology was quite different.

A significant number of new prospective cohort studies from Asia, Canada, Europe and the United States have been reported since 2005. These have provided additional evidence of the effects of long-term exposure to PM_{2.5} on mortality. Effects have now been observed at lower concentrations levels than in earlier studies, see answer to Question A5. As an example, the Pope, Ezzati & Dockery (2009) study still found significant associations between the lower PM_{2.5} concentrations in 2000 and life expectancy, despite significant gains in life expectancy associated with decreases in PM_{2.5} concentrations between 1980 and 2000. In a large Canadian study, associations persisted at very low concentrations (Crouse et al., 2012). Specifically, the effects of long-term exposure on mortality have been reported for several new cohorts (Filleul et al., 2005; Miller et al., 2007; Beelen et al., 2008a; Puett et al., 2009; Ostro et al., 2010; Lipsett et al., 2011; Crouse et al., 2012). Some cohort studies have found no associations between PM_{2.5} or particulate matter with an aerodynamic diameter smaller than 10 µm (PM₁₀) and mortality (Puett et al., 2011; Ueda et al., 2012), but these do not materially affect the overall assessment and conclusions. Regarding the European studies, the mortality risk estimated in the Dutch mortality cohort study for PM_{2.5} was 6% per 10 µg/m³ for natural-cause mortality (Beelen et al., 2008a), identical to the estimate from the American Cancer Society study (Pope et al., 2002). Furthermore, a large ecological study from Norway

reported significant associations between PM_{2.5} and cardiorespiratory mortality (Naess et al., 2007).

These Asian, Canadian, European and United States studies cover a variety of environmental settings, PM mixtures, baseline health conditions, personal characteristics and health practices. As a result, several groups of experts have determined that it is appropriate to extrapolate these findings to populations in other regions, including Europe (Cooke et al., 2007; COMEAP, 2006, 2010; Smith KR et al., 2009). The risk of ischaemic heart disease, which includes heart attacks, has particularly strong and consistent associations with PM_{2.5}. A review of most of these and related studies can be found in the United States Environmental Protection Agency (EPA) integrated science assessment for PM (EPA, 2009).

Since 2005, the evidence for a biological mechanism, derived from both epidemiological and toxicological studies, has also increased and indicates that exposure to PM_{2.5} is associated with systemic inflammation, oxidative stress and alteration of the electrical processes of the heart (Brook et al., 2010). For example, epidemiological studies now show variations in cardiovascular biomarkers of inflammation such as C-reactive protein and fibrinogen. These biomarkers have been consistently linked to subsequent cardiovascular disease and death. Long-term exposure has also been associated with preclinical markers of atherosclerosis (Künzli et al., 2005) and with progression (Künzli et al., 2010) of this pathology of high relevance to cardiovascular diseases. A series of studies from the German Heinz Nixdorf Recall Study has confirmed associations between various markers of atherosclerosis, including intima media thickness and coronary artery calcification, and the long-term average PM_{2.5} concentration and proximity to traffic in Europe (Bauer et al., 2010; Hoffmann et al., 2006, 2007). In a Belgian study, pulse pressure was associated with ambient PM_{2.5} levels among the elderly (Jacobs et al., 2012).

These and many other outcomes studied in human populations provide evidence for a pathophysiological response to current ambient concentrations of PM_{2.5}. A more complete review of the likely biological mechanisms, strongly supportive of a causal association between PM_{2.5} and cardiovascular disease and mortality, is provided by Brook et al. (2010). This review also provides a discussion of the supportive toxicological studies. The studies reporting associations with intima media thickness in human beings are supported by animal studies that show that a 6-month exposure of mice to particles results in substantial increases in atherosclerosis, compared with mice breathing filtered air (Floyd et al., 2009; Soares et al., 2009; Sun et al., 2005, 2008). The Brook et al. (2010) review contained a consensus that there was strong mechanistic evidence from animal studies of systemic pro-inflammatory responses and vascular dysfunction or vasoconstriction, supported by controlled exposure studies in human beings. The overall mechanistic evidence from animal studies was judged to be moderate for enhanced thrombosis or coagulation potential, elevated arterial blood pressure, and enhanced atherosclerosis. The overall assessment was that experimental evidence was increasingly strong, lending biological plausibility to the epidemiological findings (Brook et al., 2010).

Since 2005, further evidence has emerged of the effects of long-term exposure to fine particulate air pollution on diseases other than cardiovascular and respiratory diseases. Evidence suggests effects on diabetes, neurological development in children and neurological disorders in adults (Rückerl et al., 2011). The evidence for an association with diabetes, since the first publication (Brook et al., 2008), has been strengthened significantly. This includes epidemiological studies in Germany (Krämer et al., 2010) and Denmark (Andersen et al.,

2012a; Raaschou-Nielsen et al., 2013), supported by mechanistic studies (Basile & Bloch, 2012; Brook et al., 2012; Liu et al., 2013; Peters, 2012). A recent review of the neurological effects found in experimental and observational studies (Guxens & Sunyer, 2012) concluded that these effects were not conclusive, given the limited number of studies, their small size and their methodological constraints. Associations with PM_{2.5} include impairment of cognitive functions in adults (Ranft et al., 2009) and children (Freire et al., 2010). If these findings are corroborated by further studies, this would significantly increase the burden related to air pollution, given the increase of these diseases in ageing populations. More work is needed to disentangle which component(s) of the air pollution mixture drive the associations.

Birth cohort studies in Europe and elsewhere published since 2005 have reported significant associations between exposure to PM_{2.5} and respiratory infections and asthma in young children (Brauer et al., 2007; Gehring et al., 2010; MacIntyre et al., 2011; Morgenstern et al., 2007). Several studies have found an association between PM_{2.5} and infant bronchiolitis, an important risk for hospitalization (Karr et al., 2007, 2009a,b). Exposure to PM_{2.5} has also been linked to low lung function in 4-year-old children in a birth cohort study in the Netherlands (Eenhuizen et al., 2012), supporting previously published studies that reported effects of PM_{2.5} on lung function development, reviewed in Götschi et al. (2008). Evidence is increasing for an association of ambient air pollution, including fine particles, with birth outcomes (Parker et al., 2011; Proietti et al., 2013; Ritz & Wilhelm, 2008). A systematic review reported significant associations between exposure to PM_{2.5} and birth outcomes, including low birth weight, preterm birth and small for gestational age births (Shah & Balkhair, 2011).

The evidence for short-term effects of PM_{2.5} and PM₁₀ on mortality, morbidity and physiological end-points has also significantly increased since 2005 (Brook et al., 2010; Ruckerl et al., 2011). Several new multicity studies have confirmed the previously reported small increases (0.4–1% per 10 µg/m³) in daily mortality associated with PM_{2.5} (and PM₁₀) (Katsouyanni et al., 2009; Zanobetti et al., 2009; Ostro et al., 2006). Estimates of effects for daily mortality were similar in the United States and Europe, but somewhat larger in Canada (Katsouyanni et al., 2009). Most of the European studies are based on PM₁₀, such as the Italian EPIAIR study (Colais et al., 2012). A recent study from Stockholm reported associations of daily mortality with both PM_{2.5} and the coarse fraction of PM₁₀ (Meister, Johansson & Forsberg, 2012). A study in Barcelona also found a significant association between daily mortality and PM_{2.5}, which was further shown to differ for particles from different sources (Ostro et al., 2011). New evidence of effects on hospital admissions was based on PM₁₀ in Europe (Brook et al., 2010). A large study in the United States reported significant associations with hospital admissions for a variety of cardiovascular diseases, including ischaemic heart disease, cerebrovascular disease and heart failure (Dominici et al., 2006). For a comprehensive review, we refer to previous reviews (Brook et al., 2010; EPA, 2009; Ruckerl et al., 2011).

Question A2

What new health evidence is available on the role of other fractions or metrics of PM, such as smaller fractions (ultrafines), black carbon, chemical constituents (metals, organics, inorganics, crustal material and PM of natural origin, primary or secondary) or source types (road traffic including non-tailpipe emissions, industry, waste processing ...) or exposure times (for example, individual or repeated short episodes of very high exposure, 1 hour, 24 hours, yearly)?

Answer

Since the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006), a considerable number of new studies have been published, providing evidence on the health effects of size fractions, components and sources of PM. Health effects are observed with short-term (such as hours or days) and long-term (such as years) exposures to airborne particles.

A. Fractions or metrics of PM other than PM_{2.5} or PM₁₀

1. The 2005 global update of the WHO air quality guidelines noted that, while there was little indication that any one property of PM was responsible for the adverse health effects, toxicological studies suggested that fossil fuel and biomass combustion processes may be a significant contributor to adverse health outcomes. Since then, further information has become available to amplify the earlier conclusions. Epidemiological and toxicological studies have shown PM mass (PM_{2.5} and PM₁₀) comprises fractions with varying types and degrees of health effects, suggesting a role for both the chemical composition (such as transition metals and combustion-derived primary and secondary organic particles) and physical properties (size, particle number and surface area);
2. Three important components or metrics – black carbon, secondary organic aerosols, and secondary inorganic aerosols – have substantial exposure and health research finding associations and effects. They each may provide valuable metrics for the effects of mixtures of pollutants from a variety of sources.
 - a. New evidence links black carbon particles with cardiovascular health effects and premature mortality, for both short-term (24 hours) and long-term (annual) exposures. In studies taking black carbon and PM_{2.5} into account simultaneously, associations remained robust for black carbon. Even when black carbon may not be the causal agent, black carbon particles are a valuable additional air quality metric for evaluating the health risks of primary combustion particles from traffic, including organic particles, not fully taken into account with PM_{2.5} mass.
 - b. No new toxicological evidence has been presented to support a causal role for such inorganic secondary aerosols as ammonium, sulfates and nitrates. However, epidemiological studies continue to report associations between sulfates or nitrates and human health. Neither the role of the cations (for example, ammonium), nor the interactions with metals or absorbed components (for example, organic particles) have been well documented in epidemiological studies (see Answer C8). Even when secondary inorganic particles (especially sulphate particles) may not be the causal agents, they are a valuable additional air quality metric for evaluating health risks.

- c. There is growing information on the associations of organic carbon with health effects, and carbonaceous primary emissions are one of the important contributors to the formation of secondary organic aerosols (a significant component of the PM_{2.5} mass). The evidence is insufficient to distinguish between the toxicity of primary and secondary organic aerosols.
3. The new evidence suggests that short-term exposures to coarse particles (including crustal material) are associated with adverse respiratory and cardiovascular effects on health, including premature mortality. Data from clinical studies are scarce; toxicological studies report that coarse particles can be as toxic as PM_{2.5} on a mass basis. The difference in risk between coarse and fine PM can, at least partially, be explained by differences in intake and different biological mechanisms.
4. There is increasing, though as yet limited, epidemiological evidence on the association between short-term exposures to ultrafine (smaller than 0.1 µm) particles and cardiorespiratory health, as well as the health of the central nervous system. Clinical and toxicological studies have shown that ultrafine particles (in part) act through mechanisms not shared with larger particles that dominate mass-based metrics, such as PM_{2.5} or PM₁₀.

B. Source types

A variety of air pollution sources have been associated with different types of health effects. Most of the evidence accumulated so far is for an adverse effect on health of carbonaceous material from traffic (see also Question C1). A more limited number of studies suggest that traffic-generated dust, including road, brake and tyre wear, also contribute to the adverse effects on health.

1. Coal combustion results in sulfate-contaminated particles, for which epidemiological studies show strong evidence of adverse effects on health.
2. Sources of PM emission relevant to health also include shipping (oil combustion) power generation (oil and coal combustion) and the metal industry (such as nickel).
3. Exposure to particles from biomass combustion – most notably residential wood combustion – may be associated not only with respiratory, but also with cardiovascular health.
4. Desert dust episodes have been linked with cardiovascular hospital admissions and mortality in a number of recent epidemiological studies.

C. Exposure times – for example, individual or repeated short episodes of very high exposure, 1 hour, 24 hours, yearly

1. Epidemiological studies show further evidence that long-term (years) exposure to PM_{2.5} is associated with both mortality and morbidity. The evidence base is weaker for PM₁₀, and hardly any long-term studies are available for coarse particles.
2. There is also strong evidence from epidemiological studies that daily (24-hour average) exposures to PM are associated with both mortality and morbidity immediately and in subsequent days. Repeated (multiple day) exposures may result in larger health effects than the effects of single days.
3. While acute and long-term effects are partly interrelated, the long-term effects are not the sum of all short-term effects. The effects of long-term exposure are much greater than

those observed for short-term exposure, suggesting that effects are not just due to exacerbations, but may be also due to progression of underlying diseases.

4. There is significant evidence from toxicological and clinical studies on effects of combustion-derived particles that peak exposures of short duration (ranging from less than an hour to a few hours) lead to immediate physiological changes; this is supported by epidemiological observations.

Rationale

(a) The role of other fractions or metrics of PM

In the 2005 global update of the WHO air quality guidelines, evidence on the effects on health of different chemical constituents in PM was based on toxicological studies. An integrated science assessment for PM was published by the EPA in 2009 to support the review of the national ambient air quality standards. The integrated science assessment used evidence from both epidemiological and experimental studies to conclude that “there are many components contributing to the health effects of PM_{2.5}, but not sufficient evidence to differentiate those constituents (or sources) that are more closely related to specific health outcomes” (EPA, 2009). Despite the increased number of studies (especially epidemiological) after 2009, the general conclusion remains the same.

Black, elemental, and primary and secondary organic carbon

Black carbon concentration is usually estimated by light absorption methods that measure the light absorption of particles retained in a filter – in absorption units. On the other hand, elemental or organic carbon is determined using thermo-optical methods, also on filter samples – in mass concentration units. Black carbon absorption units can be converted to mass concentration units.

The main sources of carbon(aceous) particles are diesel powered engines, the residential burning of wood and coal, power stations using heavy oil or coal, the field burning of agricultural wastes, as well as forest and vegetation (fires). Consequently, black carbon is a universal indicator of a variable mixture of particulate material from a large variety of combustion sources and, when measured in the atmosphere, it is always associated with other substances from combustion of carbon-containing fuels, such as organic compounds (WHO Regional Office for Europe, 2012). Organic carbon not only originates from combustion, but also originates from atmospheric processes and emissions from vegetation. An example of such an organic compound is isoprene. Due to a lack of data, health studies have not been able to separate primary and secondary organic particles.

Epidemiological studies

Since the 2009 EPA integrated science assessment, a number of epidemiological studies have evaluated associations between individual constituents of PM and health. The particle constituents most often included in the studies have been sulfate and black carbon. The WHO Regional Office for Europe has recently published a report that evaluates systematically the health significance of black carbon (Janssen et al., 2012). Estimated effects on health of a 1- $\mu\text{g}/\text{m}^3$ increase in exposure were greater for black carbon particles than for PM₁₀ or PM_{2.5}, but estimated effects of an interquartile range increase were similar. Two-pollutant models in time-series studies suggested that the effect of black carbon particles was more robust than the effect of PM mass. Sufficient evidence was found for an association between daily

outdoor concentrations of black carbon and all-cause and cardiovascular mortality, and cardiopulmonary hospital admissions. Evidence was also judged sufficient for an association between long-term black carbon concentration and all-cause and cardiopulmonary mortality.

There are, typically, considerable intercorrelations between particle constituents in ambient air, especially between constituents from the same source. This is only one reason why the detection of associations in epidemiological studies is not enough to judge causality. The WHO Regional Office for Europe report on black carbon concluded that black carbon per se may not be responsible for the observed health effects, but that black carbon could be interpreted as an indicator for a wide variety of combustion-derived chemical constituents (WHO Regional Office for Europe, 2012). The more robust associations observed for black carbon than for PM_{2.5} in two-pollutant models in short-term epidemiological studies were interpreted to suggest that black carbon is a better indicator of harmful particle substances from combustion than is total particle mass.

Organic carbon has been included in epidemiological studies less often than black carbon. In most studies published after the 2009 EPA integrated science assessment, (total) organic carbon has been found to be associated with short-term changes in cardiovascular (Delfino et al., 2010a; Ito et al., 2011; Kim et al., 2012; Son et al., 2012; Zanobetti et al., 2009) and respiratory health (Kim et al., 2008), or with changes in the levels of inflammatory markers (Hildebrandt et al., 2009).

In epidemiological studies, the effects of combustion-derived organic carbon are difficult to separate from those of black carbon and/or elemental carbon because of a high correlation due to the common source: combustion processes (WHO Regional Office for Europe, 2012). Elemental carbon is most strongly associated with primary combustion particles and primary organic carbon, whereas secondary organic aerosol formation is delayed with respect to the primary emissions, because secondary organic carbon is formed during longer range transport in the atmosphere. Secondary organic carbon also has a significant biological component, but this part of PM has hardly been studied in relation to health effects. A series of panel studies have reported that while total organic carbon has not been associated with the outcomes, associations have been observed for primary organic carbon (and not secondary organic carbon compounds) (Delfino et al., 2009b; 2010a; 2011). In one study, primary organic carbon was associated with markers for systemic inflammation, whereas secondary organic carbon was associated with a marker for pulmonary inflammation (Delfino et al., 2010b).

Only one study, since the 2005 global update of the WHO air quality guidelines, has evaluated associations between long-term exposure to organic carbon and health (Ostro et al., 2010). For organic carbon, associations were observed for both ischaemic heart disease and pulmonary mortality, whereas elemental carbon was only associated with ischaemic heart disease mortality. It should be noted that organic carbon is a very complex mixture of primary and secondary organic aerosols that may contain specific components with important health outcomes, such as hazardous air pollutants (HAPs); thus, the health impact of organic carbon may greatly vary from site to site and time to time

Clinical studies

Healthy human subjects exposed for 2 hours to ultrafine clean – that is without any components adsorbed on the surface – carbon particles at concentrations of 10 µg/m³ and 25 µg/m³ showed a high overall deposition fraction in the respiratory system (0.66 ± 0.12 at rest; mean ± SD) which increased with exercise (0.83 ± 0.04; mean ± SD) (Frampton, 2001).

Asthmatic subjects showed an even higher deposition (0.76 ± 0.05) than did healthy subjects while breathing at rest (Frampton et al., 2004). The effects of ultrafine carbon particles were observed in both heart rate variability and cardiac repolarization, but there were no changes in soluble markers of either systemic inflammation or coagulation. In a more recent study, no vascular impairment or effect on blood clotting were observed in volunteers exposed for 2 hours to $70 \mu\text{g}/\text{m}^3$ of ultrafine carbon particles (Mills et al., 2011). In this same study, and in Lucking et al. (2011), it was shown that removing the particles from diluted diesel engine exhaust also prevented adverse effects on the cardiovascular system. The difference is explained by the differences in composition, with black carbon particles (soot) being rich in (semi)volatile organic particles and metals. There are no studies reported that used exposure periods longer than 2 hours.

Toxicological studies

Inhalation of ultrafine carbon particles (38 nm, $180 \mu\text{g}/\text{m}^3$ for 24 hours) caused increased heart rate and decreased heart-rate variability in rats, but there was no inflammatory response and no change in the expression of genes having thrombogenic relevance (Harder et al., 2005). In spontaneously hypertensive rats exposed to similar ultrafine carbon particles ($172 \mu\text{g}/\text{m}^3$ for 24 hours), blood pressure and heart rate increased with a lag of 1–3 days. Inflammatory markers in lavage fluid, lung tissue, and blood were unaffected, but mRNA expression of hemeoxygenase-1, endothelin-1, endothelin receptors, tissue factor, and plasminogen activator inhibitor in the lung showed a significant induction (Upadhyay et al., 2008), which is an indication of a cardiovascular (or even systemic) effect without adverse effects at the port of entry – that is, the lung. Given differences in the deposited dose in the respiratory systems of rats and human beings, the concentration used in this study is high, but not unrealistic when extrapolated to human exposures. Yet, clean carbon particles alone are unlikely to result in detrimental effects at current outdoor levels. Although not a true toxicological study, Biswas et al. (2009) were able to demonstrate that a substantial portion of soot-induced reactive oxygen production (associated with oxidative stress and inflammation) could be attributed to the (semi)volatile organic fraction on the carbon particle core, suggesting that organic particles otherwise not recognized as PM can be responsible for a substantial part of the toxicity of the carbonaceous fraction of PM.

Likewise, but not yet studied, other particles (such as sulfates) may also act as carriers. Verma et al. (2009b) have shown, for Los Angeles in summer, that both primary and secondary organic particles possess high redox activity; however, photochemical transformations of primary emissions with atmospheric ageing potentially enhance the toxicological potency of primary particles, in terms of generating oxidative stress and leading to subsequent damage in cells.

The WHO Regional Office for Europe review (2012) concluded that black carbon particles may not be a major direct toxic component of fine PM, but it may operate as a universal carrier of a wide variety of chemicals of varying toxicity to the lungs, the body's major defence cells and (possibly) the systemic blood circulation.

Coarse particles

The number of studies on the health effects of PM_{10} is vast, and the number of studies on $\text{PM}_{2.5}$ is increasing rapidly. In the 2005 global update of the WHO air quality guidelines, it was noted that, for coarse particles ($\text{PM}_{10-2.5}$), there was only limitedly epidemiological data. The availability of epidemiological data has significantly increased since 2005. In 2009, the

EPA integrated science assessment concluded – based on data from epidemiological, controlled human exposure, and toxicological studies – that there was “suggestive evidence of a causal relationship between short-term exposure to coarse PM and cardiovascular and respiratory health effects and mortality”. The integrated science assessment further stated that there was “not sufficiently evidence to draw conclusions on the health effects of long-term exposure to coarse PM”. Since 2009, evidence of the short-term effects of coarse particles on cardiorespiratory health and mortality has increased significantly.

Epidemiological studies

The latest systematic review by Brunekreef & Forsberg (2005) made the scientific community aware again of the potential health risks associated with coarse particles. The review concluded that coarse PM has at least as strong short-term effects on respiratory health as PM_{2.5}; also, for cardiovascular effects, some supportive evidence was found. For mortality, evidence was concluded to be stronger for PM_{2.5}. The few long-term studies did not provide any evidence of an association with potential health risks.

Taking into account the newest evidence on the effects of coarse PM on cardiorespiratory health (Chen et al., 2005; Halonen et al., 2008, 2009; Peng et al., 2008; Perez et al., 2009a; Zanobetti et al., 2009), the EPA integrated science assessment for PM concluded that, in general, short-term epidemiological studies reported positive associations between mortality and cardiovascular and respiratory hospital admissions (EPA, 2009). For cardiovascular outcomes (admissions and physiological effects), effect estimates of coarse PM were found to be comparable to those of PM_{2.5}. On the other hand, it was noted that studies on respiratory admissions were conducted in a limited number of areas, and no associations of coarse PM on lower respiratory symptoms, wheeze, or medication use were reported (in panel studies). Published after the integrated science assessment, one study reported associations between daily coarse PM concentrations and wheeze in children with asthma (Mann et al., 2010).

After the 2009 EPA integrated science assessment, several new studies reported associations between coarse particles and cardiovascular (Atkinson et al., 2010; Chen R et al., 2011; Malig & Ostro, 2009; Mallone et al., 2011), respiratory (Chen R et al., 2011) or total mortality (Meister, Johansson & Forsberg, 2012; Tobías et al., 2011). Expanding the geographical spread of studies on respiratory admissions, a study in Hong Kong (Qiu et al., 2012) reported positive associations between coarse PM and (total) respiratory, asthma, and chronic obstructive pulmonary disease admissions. Effect estimates for coarse PM were somewhat lower than those for PM_{2.5}, and in two-pollutant models they decreased more than the estimates for PM_{2.5}; yet the associations remained for respiratory and chronic obstructive pulmonary disease admissions.

It should be noted that in the Hong Kong study, as in most of the studies, coarse PM was calculated by subtracting measured PM_{2.5} from measured PM₁₀. This means that there is more measurement error for coarse PM than for PM_{2.5}, which would make associations between coarse PM and health more difficult to find – an issue brought up also by the integrated science assessment. Compared with fine particles, coarse particles also vary more spatially and infiltrate less efficiently into indoor air, which makes further assessment of exposure to coarse PM in epidemiological studies more challenging.

After the EPA integrated science assessment, only two studies were published on the long-term effects of coarse PM; both of them were conducted in the United States and used the same models to estimate concentrations of coarse PM. In the first study (Puett et al., 2009),

coarse PM was not associated with mortality or coronary heart disease incidence among women in two-pollutant models. In the second one (Puett et al., 2011), there was limited evidence of coarse PM having an effect on cardiovascular health among men, mainly on the incidence of ischaemic stroke.

The EPA noted in the 2009 integrated science assessment that the composition of coarse PM can vary considerable between cities, but that there is limited evidence on the effects of the various biological and chemical components of coarse PM. However, there is one source of coarse PM for which evidence has started to accumulate – desert dust, which consists mainly of crustal material (see the dedicated paragraph under the heading “(b) The role of source types”).

Practically no studies compare the effects on health of coarse PM from different sources. One study included source-specific PM₁₀: exhausts, fuel oil combustion, secondary nitrate and/or organic particles, minerals, secondary sulfate and/or organics and road dust had statistically significant associations with all-cause and cardiovascular mortality (Ostro et al., 2011). At high latitudes, the levels of road dust are at their highest during wintertime, when studded tires are in use and the roads are sanded to increase friction. In a recent mortality study conducted in Stockholm, Sweden, effect estimates for coarse PM were slightly higher during wintertime than during other times of the year (Meister, Johansson & Forsberg, 2012).

Clinical studies

Although not a direct comparison, Graff et al. (2009) arrived at the conclusion that, in their studies of human beings (2 hours, 90 µg/m³), exposure to coarse PM produces a measurable mild physiological response in healthy young volunteers that is similar in scope and magnitude to that of volunteers exposed to fine PM, suggesting that both size fractions are comparable in inducing cardiopulmonary changes in acute exposure settings. No other new evidence since 2005 has been published.

Toxicological studies

Very few studies have compared the toxicity of coarse PM (10–2.5 µm) and fine PM (smaller than 2.5 µm). The few studies available usually collected PM on filters and used in vitro assays or intratracheal exposures to assess the relative hazard, often in relation to the sources of emission. Since the inhalability and, therefore, the deposition efficiency in the respiratory tract of coarse particles is substantially lower, the interpretation of the risk of coarse versus fine PM has to be considered in that context. This also explains the lack of experimental inhalation studies of coarse particles. Wegesser, Pinkerton & Last (2009) compared these two fractions, collected during wildfires in California, and concluded that the hazard expressed per unit mass is roughly the same – with some evidence that fine PM is more toxic in terms of inflammatory potential and cytotoxic responses. In a different study, these effects were attributed to the insoluble components of the mixture and are not caused by an endotoxin (Wegesser & Last, 2008). The intratracheal exposures in rats and mice, as well as in vitro studies, suggest that similar effects can be observed for coarse and fine PM in the bioassays of lung cells (Gerlofs-Nijland et al., 2007; Halatek et al., 2011; Gilmour et al., 2007; Jalava et al., 2008; Happonen et al., 2010) and that coarse PM can be even more hazardous than fine PM. Again, given that the deposition efficiency and pattern of coarse and fine PM differ largely, the health outcomes in a population can differ at equal mass exposures.

Ultrafine particles

There is a general consensus that ultrafine particles are defined as particles smaller than 100 nm in mobility diameter and mostly stem from combustion processes in urban settings (Peters, R ckerl & Cyrus, 2011). Emitted primary ultrafine particles are transformed rapidly due to coagulation, adsorption and secondary particle formation. Also, new particle formation takes place in the atmosphere and may give rise to a high number concentration of particles in the nucleation and Aitken modes (0–20 nm and 20–100 nm). This is of special relevance in areas (urban, industrial and rural) with high photochemistry (Reche et al., 2011). Therefore, ultrafine particles have greater spatial and temporal variability than the fine particle mass concentrations. Typically, they are characterized by particle number concentration, which is the metric most measurement devices employ. Research on nano-size material is applicable to assessing the potential toxicity of ultrafine particles and has shown that not only their size, but also their composition, surface chemistry and surface charge are important (Bakand, Hayes & Dechsakulthorn, 2012). Although ultrafine particles are defined by size and number, this fraction may contain such components as metals and polycyclic aromatic hydrocarbons. The following discussion is based on their physical properties only.

Epidemiological studies

Based on epidemiological studies, there is still limited evidence on the effects on health of ultrafine particles (R ckerl et al., 2011), although the potential for such effects was considered to be large in a recent synthesis of opinions of experts (Knol et al., 2009).

Compared with the assessment in the 2005 global update of the WHO air quality guidelines, links were observed between daily changes in ultrafine particles and cardiovascular disease hospital admissions, as well as cardiovascular disease mortality (Hoek et al., 2010). A link between ultrafine particles or total number concentrations and cardiovascular disease hospital admission was observed in European multicentre studies (von Klot et al., 2005; Lanki et al., 2006) as well as in some single-city analyses (Andersen et al. 2008a, 2010; Franck et al., 2011). The evidence for respiratory hospital admissions was mixed (Andersen et al., 2008a; Leitte et al., 2011; Iskandar et al., 2012; Leitte et al., 2012). The link between ultrafine particles or total number concentrations and natural cause mortality appeared to be more robust in time-series analyses (Berglind et al., 2009; Breitner et al., 2009; Atkinson et al., 2010).

Links between daily changes in ultrafine particles and markers of altered cardiac function, inflammation and coagulation were suggested by several, but not all, studies (see reviewed studies within R ckerl et al. (2011) and Weichenthal (2012)) and were further supported by recently published studies (Rich et al., 2012b).

Clinical studies

A few recently published clinical studies support pre-2005 studies that suggested increasing evidence for ultrafine particles in eliciting health effects during and after 2-hour exposure periods (Mills et al., 2007; Langrish et al., 2009; Mills et al., 2011). However, most studies were performed with a mixture of particles and gases, which do not allow statements to be made about the contributions of ultrafine particles. In the clinical setting, the removal of very high particle numbers by filters prevented the otherwise occurring arterial stiffness and increases of blood clotting (Br uner et al., 2008). Similar observations were made in health

subjects and patients with coronary heart disease that were wearing a very simple, yet highly efficient face mask while walking in highly polluted areas in Beijing, China (Langrish et al., 2009). Observations in healthy young volunteers exposed to pure elemental carbon particles implied that heart function was not affected by these controlled exposures. This was confirmed by a very similar exposure in a study (Mills et al., 2011) that looked at measurements of arterial stiffness and blood clotting in healthy subjects. The presence of a susceptible population has not been shown, and no studies could be identified that have applied exposure periods longer than 2 hours.

Toxicological studies

Substantial advances have been made in understanding the action of ultrafine particles. Ultrafine particles have the ability to translocate from the alveolar space into tissues and to spread systemically, reaching many organs, including the heart, liver, kidneys and brain (Kreyling, Hirn & Schleh, 2010). Ultrafine particles exhibit systemically a multitude of biological responses due to their reactive surfaces within human beings (Bakand, Hayes & Dechsakulthorn, 2012). The study of ultrafine particle toxicology has made substantial advances, as properties of particles smaller than 100 nm are intensively studied for engineered nanoparticles. Specific toxicological actions include impairment of phagocytosis and breakdown of defence mechanisms, crossing tissues and cell membranes, injury to cells, generation of reactive oxygen species, oxidative stress, inflammation, production of cytokines, depletion of glutathione, mitochondrial exhaustion, and damage to protein and DNA, most of which also occurs with larger size PM (Bakand, Hayes & Dechsakulthorn, 2012). Biodistribution studies also suggest that the effects of ultrafine particles may very well be observed in organs other than those that correspond to the port of entry – for example, the central nervous system (Kleinman et al., 2008; Kreyling et al., 2013). In light of different biodistributions on inhalation and the likelihood that ultrafine particles can escape natural defence mechanisms, such as phagocytosis, it is likely that ultrafine particles will also be linked to biological pathways and responses that differ from larger size particles (fine and coarse PM).

Secondary inorganic aerosols

Sulfate is a major component, together with nitrate, of secondary inorganic particles that are formed from gaseous primary pollutants. Because of their high solubility (and low hazard) and their abundance in the human body, these secondary inorganic particles have been suggested to be less harmful than, for example, primary combustion-derived particles (Schlesinger & Cassee, 2003).

Epidemiological studies

It was noted in the 2009 EPA integrated science assessment that secondary sulfate had been associated with both cardiovascular and respiratory health effects in short-term epidemiological studies. At that time, there were more studies available that looked at the cardiovascular effects of PM constituents and sources than at the respiratory effects. Since the integrated science assessment, epidemiological evidence has continued to accumulate on the short-term effects of sulfate on both cardiovascular (Ito et al., 2011) and respiratory (Atkinson et al., 2010; Kim et al., 2012; Ostro et al., 2009) hospital admissions; two studies have linked sulfate also with cardiovascular mortality (Ito et al., 2011; Son et al., 2012). There is also some new evidence on the associations between daily increases in ambient sulfate and physiological changes related to cardiovascular diseases, such as ventricular arrhythmias and endothelial dysfunction (Anderson et al., 2010; Bind et al., 2012).

It should be noted that, similar to black carbon, sulfate is associated with a number of other constituents from the combustion of fossil fuels, such as transition metals and organic compounds. In many areas, sulfates and nitrates are associated with hydrogen and ammonium. Sulfate could be considered to be an indicator of harmful constituents from oil and coal combustion. On the other hand, the situation may be more complex: sulfate has been reported to increase the solubility of iron (Oakes et al., 2012), which may increase the harmfulness of particles. The follow-up study of the Harvard Six Cities Study reported that there was no evident increase in the estimate of the effect of $PM_{2.5}$ mass over time, despite the relatively higher drop in sulfate concentrations, when compared with $PM_{2.5}$ mass during the study period (Lepeule et al., 2012). This suggests that sulfate does contribute to the toxicity of ambient PM. In any case, it is still unclear whether removal of SO_2 (a precursor for sulfate) from the emissions of oil and coal combustion would lead to a significant reduction in the health effects associated with these sources. Also, it is accepted that if new particle formation of sulfuric acid or ammonium sulfate occurs in the atmosphere, these new particles may act as a condensation sink for primary and secondary organic components.

Nitrate is one more indicator of emissions from combustion processes, including traffic exhausts that are rich in oxides of nitrogen. In a mortality study conducted in Seoul, Republic of Korea, there was some evidence of cardiovascular, but not respiratory, effects for nitrate, and even more so for ammonium (Son et al., 2012). In contrast, two studies on hospital admissions found evidence of respiratory, but not cardiovascular, effects for nitrate (Atkinson et al., 2010; Kim et al., 2012). It is noteworthy, in these studies, that sulfate was not associated with cardiovascular admissions, showing that the recent evidence for sulfate is not fully consistent.

Only one recent study has evaluated associations between long-term exposure to nitrate and health. In a study conducted in California (Ostro et al., 2010), both nitrate and sulfate were associated with cardiopulmonary mortality. Sulfate and organic carbon also showed consistent associations in multipollutant models. Multiple analyses of prospective cohort studies in the United States have also associated long-term exposure to sulfate with mortality (Smith KR et al., 2009).

Clinical and toxicological studies

No new relevant evidence or relevant information on the role of secondary inorganic aerosols has been reported since the review by Schlesinger & Cassee (2003), in which it was concluded that these particles have little biological potency in normal human beings or animals or in the limited compromised animal models studied at environmentally relevant levels. As mentioned in Reiss et al. (2007), toxicological evidence provides little or no support for a causal association between particulate sulfate compounds and a risk to health at ambient concentrations. Limited toxicological evidence does not support a causal association between particulate nitrate compounds and excess health risks either. However, it cannot be excluded that the cations associated with sulfates and nitrates (such as transition metals, acidity marked by hydrogen cations), nor absorbed components (such as organic particles) may be the underlying cause of the strong associations between sulfate and health effects, because ammonium sulfate or ammonium bisulfate can be regarded as a relative low toxic material, in comparison with transition metals or polycyclic aromatic hydrocarbons. No toxicological studies have been published that investigated the role of sulfates (or nitrates) in the complex mixture of PM; at present, it cannot be excluded that these secondary inorganic components have an influence on the bioavailability of other components, such as metals.

Transition metals and metal compounds

Epidemiological studies

A few panel and population studies published during or after 2009 have included transition metals (Bell et al., 2009a; de Hartog et al., 2009; Ito et al., 2011; Mostofsky et al., 2012; Ostro et al., 2009, 2010; Suh et al., 2011; Zanobetti et al., 2009; Zhou et al., 2011). A comparison of the relative harmfulness of different metals is not possible at this point, because most of the studies have included only a few transition metals, most often zinc or nickel, and there is substantial variability in the outcomes available. Furthermore, no patterns emerge for transition metals as a general category: depending on the study and outcome, associations may have been found for all, a few, or no metals. Most evidence has been found for an association between nickel and cardiovascular hospital admissions (Bell et al., 2009a; Ito et al., 2011; Mostofsky et al., 2012; Zanobetti et al., 2009).

Clinical studies and toxicological studies

Metal oxides are substances traditionally considered to be relatively inert chemically. However, in very small (ultrafine) size ranges, these particles have been linked with significant oxidative stress mediated toxicity (Duffin, Mills & Donaldson, 2007). Some metals, such as zinc oxide, will dissolve in the body (Gilmour et al., 2006; Charrier & Anastasio, 2011). Zinc ions have many physiological functions, but they can also interfere with the body's homeostasis, leading to such adverse effects as oxidative stress and inflammation. Toxicological examinations of the constituents of ambient air have not identified an individual metal as being a likely cause of human health problems associated with PM (Lippmann et al., 2006; Lippmann & Chen, 2009). A study by Lippmann et al. (2006) did involve 6 months of weekday concentrated ambient particle exposures, in which an association between cardiac function changes and nickel was also observed for short-term responses to pronounced daily peaks in nickel. In this and subsequent subchronic concentrated ambient particle exposure studies, there was no evidence of an association of nickel with chronic effects. Moreover, controlled exposure of young, healthy adults to PM_{2.5} caused an elevation in blood fibrinogen at 18 hours post-exposure. This response was correlated with a copper–zinc–vanadium factor in the PM. In healthy elderly adults, PM_{2.5} exposures decreased heart rate variability, a response not seen in young adults (Devlin et al., 2003).

In Toronto, there was a PM_{2.5}-related mean decrease in brachial artery diameter, but no changes in blood pressure in one study; in a follow-up study, involving most of the same subjects, PM_{2.5} exposure produced a significant decrease in diastolic blood pressure. In both studies, the effects were significantly associated with organic carbon. There were suggestive, but not significant, associations with elemental carbon and some metals (cadmium, potassium, zinc, calcium and nickel) in the first study (Urch et al. 2005). In their review, Lippmann & Chen (2009) concluded that if there are health-related effects of specific metals, other than the effects of nickel in ambient fine PM on cardiac function, they are not yet known. Overall, it appears that the cardiovascular effects of ambient air PM_{2.5} are greatly influenced, if not dominated, by their metal contents, especially the transition metals, and that nickel is likely to be a key component (Lippmann & Chen, 2009). An important role for metals is also evident in a study in which a single dose of dusts from two types of tyre were instilled intratracheally in the lungs of rats, and effects were assessed within 24 hours and after 4 weeks. One dust was made from ground tyres of recycled styrene butadiene rubber, while a second dust was made from scrap tyres. Tests were done with administered saline, the

two tyre dusts, and soluble zinc, copper, or both. At very high dose levels (5 mg/kg rat), the exposures induced cardiac oxidative stress (Gottipolu et al., 2008), which was associated with the water soluble zinc and copper.

Despite the toxicological evidence that controlled exposure studies using transition metals can result in detrimental health effects, it is unlikely that these components can explain all of the health effects observed in epidemiological studies at present ambient levels. However, transition metals remain a group of components for which reduction measures will most likely lead to improving the health status of the population.

(b) The role of source types

Extreme caution is required when attributing health effects to sources based on health impact assessment studies that use specific components of PM. For example, when taking black carbon as an indicator in a health impact assessment, to obtain concentration–response functions in Europe, caution is required when attributing health outcomes to sources. Thus, in many cases most black carbon would be attributed to diesel exhaust emissions, but attributing the whole health impact to diesel would be erroneous. This is because several sources, such as gasoline engines and other sources co-emitting with diesel exhaust or varying collinearly with black carbon due to meteorology, would be included – simply because they correlate with black carbon. This is an important limitation when dealing with source-related health outcomes.

The 2005 global update of the WHO air quality guidelines considered the effects on health of particles from biomass combustion in a separate chapter, because of the significance of biomass combustion as an emission source. Therefore, special emphasis has been given to the issue in this review. A WHO workshop in Bonn concluded in 2007 that current knowledge does not allow specific quantification of the health effects of emissions from different sources (or of individual components). In 2009, the EPA integrated science assessment concluded that “there are many components contributing to the health effects of PM_{2.5}, but not sufficient evidence to differentiate those sources (or constituents) that are more closely related to specific health outcomes”. The integrated science assessment further noted that a number of source types – including motor vehicle emissions, coal combustion, oil burning, and vegetative burning– are associated with health effects and went on to include crustal material as another potentially toxic component. The limited new evidence accumulated after 2009 does not lead to changes in the conclusions.

New epidemiological evidence on the health relevance of various particle sources has come from two types of studies: some studies have simply included chemical constituents known to be indicators of specific sources; others have used statistical source-apportionment techniques to partition the mass of particles between sources. Most studies have been able to identify emission sources for traffic, crustal material, and secondary inorganic aerosols (as indicated by sulfate or nitrate). Depending on location, and monitoring tools also, sources for biomass combustion, industry, oil combustion, coal combustion, cooking, hydrogenated organic aerosols, oxygenated organic aerosols and sea spray may have been identifiable.

Traffic

Traffic is not only a source of combustion particles, but is also a source of road dust that originates from the wear of road surfaces, brakes, clutches and tyres. Simultaneous emissions of gaseous pollutants and noise make estimation of traffic-related PM effects a challenge. The

relative importance of all types of pollutants originating from traffic will be considered in the Answer for Question C1.

Epidemiological studies

Vehicular traffic does not have a unique indicator, but road traffic (especially vehicles powered by diesel fuel) is a major source of black carbon in most urban environments. Consequently, evidence accumulated after 2005 on the health effects of black carbon indicates that both short-term and long-term exposures to particles in vehicle exhausts are harmful. In the more limited number of short-term studies that have been based on source apportionment, PM_{2.5} from traffic has typically been found associated with cardiovascular (de Hartog et al., 2009; Cakmak et al., 2009; Lall, Ito & Thurston, 2011; Lanki et al., 2006; Mar et al., 2006; Ostro et al., 2011; Sarnat et al., 2008; Yue et al., 2007) and respiratory health (Cakmak et al., 2009; Gent et al., 2009; Penttinen et al., 2006; Sarnat et al., 2008), but not always (Jacquemin et al., 2009; Lall, Ito & Thurston, 2011; Schreuder et al., 2006).

The source category of “crustal material” can be assumed to consist of substantial amounts of road dust, although in some locations natural sources may be important too. Some research groups have even named the source category for crustal material “road dust”. The results for crustal material and/or road dust have been slightly less consistent than those for vehicular exhausts. In some studies, the source has been associated with cardiovascular (Andersen et al., 2007; Cakmak et al., 2009; Ito et al., 2006; Ostro et al., 2011; Yue et al., 2007) or respiratory health (Cakmak et al., 2009; Gent et al., 2009). However, there are also studies without evidence of cardiovascular (Lanki et al., 2006; Mar et al., 2006) or respiratory effects (Jacquemin et al., 2009; Lall, Ito & Thurston, 2011; Schreuder et al., 2006).

Only a few of these studies were published after 2009 – that is they have not affected the formulation of the integrated science assessment. In New York City, traffic was associated with cardiovascular hospital admissions, but no effect was observed for soil particles (Lall, Ito & Thurston, 2011). A study conducted in Barcelona, Spain, associated separately PM_{2.5} from road dust and mineral dust, and vehicle exhausts with daily all-cause mortality (Ostro et al., 2011). The health outcomes of the contributions of these components were higher than the ones obtained for the PM_{2.5} bulk mass concentrations.

Some recent studies have linked PM_{2.5} from traffic with birth outcomes. Wilhelm et al. (2012) found both diesel and gasoline PM_{2.5} and geological PM_{2.5} to be associated with low birth weight. The same study group found preterm birth to be associated with diesel PM_{2.5} (but not other categories of traffic PM). Bell et al. (2010) reported motor vehicles and road dust to be associated with lower birth weight.

In conclusion, the evidence on the harmfulness of particles from traffic has increased substantially since the 2005 global update of the WHO air quality guidelines. However, because of limited data and large variability in outcomes and available source indicators and/or categories, traffic cannot be ranked yet relative to other particle sources with respect to harmfulness. The review by Stanek et al. (2011b) concluded that PM_{2.5} from crustal or combustion sources, including traffic, may be associated with cardiovascular effects; for respiratory effects, the evidence for association was judged limited.

Clinical and toxicological studies

Diesel engine exhaust is rich in PM, mostly below 2.5 μm . A large database describes all sorts of adverse health effects due to exposure to diesel engine exhaust. Exposure to diesel engine exhaust in healthy volunteers causes inflammation of the airways (Behndig et al., 2006) and reduces vascular function (Mills et al., 2005). In patients with heart problems (stable myocardial infarction), diesel engine exhaust causes myocardial ischaemia and reduces the clot resolving function (endogenous fibrinolytic capacity) (Mills et al., 2007). Although in certain urban areas diesel engine exhaust particles can be a substantial part of the total PM to which people are exposed, it is not clear if diesel engine exhaust is always more potent than PM on a mass basis. For example, diesel engine exhaust (105 $\mu\text{g}/\text{m}^3$) appeared to be less toxic in inducing plaque development than corresponding exposures to $\text{PM}_{2.5}$ (105 $\mu\text{g}/\text{m}^3$, 4 days/week, 5 months), indicating that some components in ambient $\text{PM}_{2.5}$, which are not present in diesel engine exhaust, are responsible for exacerbating plaque progression (Quan et al., 2010). In their recent review, McClellan, Hesterberg & Wall (2012) pointed out that, although there are good reasons for concern for health effects due to diesel engine exhaust exposure, significant efforts have been made to abate the composition of diesel engine exhaust in the past few decades, resulting in a more fuel efficient and complete combustion process and the installation of filter traps with substantial lower mass emissions. It seems very likely that this will have a profound effect on the toxicity of diesel engine exhaust, but there is no systematic review available that allows clear conclusions on an increase or decrease of the toxic potency and associated health risks.

Apart from the changing technologies, the composition of the fuel is also changing, by using biodiesel blends. There is a large knowledge gap with respect to the health effects related to replacing petroleum-based diesel with biodiesel fuel. There is conflicting evidence about the extent to which biodiesel fuel exhaust emissions present a lower risk to human health relative to petroleum-based diesel emissions (Swanson, Madden & Ghio, 2007). German studies have shown significantly increased mutagenic effects, by a factor of 10, of the particle extracts from rapeseed oil in comparison to fossil diesel fuel; and the gaseous phase caused even stronger mutagenicity (Bünger et al., 2007). Biodiesel (rapeseed oil methyl ester) has been shown to have four times higher cytotoxicity than conventional diesel under idling conditions, while no differences were observed for the transient state (Bünger et al., 2000). So far, the opposite was found by others: no differences for cytotoxicity with vehicle emissions under idling conditions (Jalava et al., 2010).

Comparing different studies to determine the possible adverse effects on health of biofuels is difficult, since all studies have been performed under different conditions. It has been seen that the emissions, as well as the health effects related to changes in emission substances or concentrations, are influenced by: the type of vehicle and/or motor used for the study; which test cycle is run; if the subsequent exhaust is diluted from the tailpipe or not and differences in fuel type; and fuel quality. Within the North American Electric Reliability Corporation programme, various sources of particle emissions were tested for their toxicological profile. For example, $\text{ApoE}^{-/-}$ mice were exposed by inhalation 6 hours a day for 50 consecutive days to multiple dilutions of diesel or gasoline exhaust, woodsmoke, or simulated *downwind* coal emissions. From Lund et al. (2007), as well as a meta-analysis by Seilkop et al. (2012), it can be concluded that filtration of particles has little effect on responses – that is, particulate components ranked third to seventh in predictive importance for the eight response variables. This suggests that not only the particles, but certainly also the gaseous fraction of engine exhaust is related to adverse health effects. Although it is beyond the scope of the question,

these observations, as well as those reported from clinical studies by Mills et al. (2005, 2007) mentioned above, point out that exhaust control strategies need to be evaluated for the likely hazard of the remaining mixture of components: a reduction of PM mass may not be accompanied by a similar trend in the reduction of toxicity.

Recent toxicological studies suggest that both tailpipe and non-tailpipe emissions (brake wear and tyre dust) express toxic properties that are similar or sometimes stronger on a per milligram basis than those found for diesel engine soot, for example. This will be discussed in section C1.

Coal and oil combustion

Epidemiological studies

After 2005, only one published epidemiological study based on source apportionment has included a category for coal combustion. Research teams found some evidence of an effect on total and cardiovascular mortality in Washington, DC (Ito et al., 2006). In another study, selenium, an indicator element for emissions from coal combustion, was found to be associated with cardiovascular mortality and hospital admissions in New York City (Ito et al., 2011).

The few epidemiological studies that included an oil combustion source provided conflicting results on the effects of the emissions on respiratory and cardiovascular health: some studies reported an effect (Andersen et al., 2007; Gent et al., 2009; Ostro et al. 2011) whereas others did not (Ito et al., 2006; Lall, Ito & Thurston, 2011; Lanki et al., 2006). Sometimes no effect was observed for oil combustion, as obtained from source apportionment, but an effect existed for vanadium, an indicator element for emissions from oil combustion (Bell et al., 2010; de Hartog et al., 2009).

It should be noted that the source category “secondary inorganic particulate air pollution” (typical indicator is sulfate) has been associated with cardiorespiratory health in most studies published since 2005. The category includes particles from coal and oil combustion, since vanadium and nickel (tracers of heavy oil combustion) are often found in this association with secondary sulfate (Viana et al., 2008, a paper on source apportionment in Europe), but also includes particles from vehicle exhausts.

Toxicological studies

Several studies based in the United States have reported toxicological evaluations of short-term exposure to coal-fired power plant emissions (Godleski et al., 2011). In general, these emissions – weather aged and/or oxidized, and diluted or not – showed very little (if any) adverse effects in rat’s responses to the inhaled aerosols studied. Godleski et al. (2011) also reported that no specific toxic constituent could be identified that explained the subtle effects. Barrett et al. (2011) reported that downwind coal combustion emissions are able to exacerbate various features of allergic airway responses, depending on the timing of exposure in relation to allergen challenge, and that these symptoms were related to both the particulate and gaseous phase of the emissions. A large number of studies have been published on residual oil fly ash PM. This type of dust is rich in transition metals (see section on “Transition metals and metal compounds” above), such as vanadium and nickel, all of which possess strong redox activity associated with the ability to cause oxidative stress.

Industry

Epidemiological studies

Obviously, a heterogeneous group of emission sources can be referred to as *industry*; and, consequently, the source category “industry” differs between epidemiological studies. Depending on location, the category might consist of one dominant source, or be a mixture of industrial sources or even other combustion sources. Eight short-term epidemiological papers published since 2005 have included a source category (or several) for industry.

In papers based on the ULTRA Study conducted in three European cities, industry was not associated with harmful physiological changes (Jacquemin et al., 2009; Lanki et al., 2006; de Hartog et al., 2009). Lall, Ito & Thurston (2011) reported a source category called “steel metal works” to be associated with respiratory, but not cardiovascular, hospital admissions in New York City. In contrast, in Atlanta, Georgia, a source category “metal processing” was associated with cardiovascular, but not respiratory, admissions (Sarnat et al., 2008). Concerning mortality, emissions from incinerators in Washington, DC, or from the industry sector in Barcelona (Spain) were not associated with total or cardiovascular mortality (Ito et al., 2006; Ostro et al., 2011), whereas emissions from copper smelters were associated with both (Mar et al., 2006).

A few recent studies have looked at the long-term effects of emissions from industry, by linking distance from one or several point sources with health. The problem in most of these studies has been the lack of individual level adjustment for confounders. In some studies, even area level adjustment was not conducted (excluded from this review). Furthermore, it is seldom possible to separate between the effects of particles and gaseous pollutants. No general conclusions can be made based on the limited new data.

In a study by Monge-Corella et al. (2008), proximity to the paper, pulp or board industries was not associated with lung cancer mortality in Spain. Living near a nickel and/or copper smelter was reported to be associated with increased cardiovascular mortality in Harjavalta, Finland (Pasanen et al., 2012). An estimate of long-term exposure in the study was based on levels of nickel in soil humus. The result should be interpreted cautiously because the highest emissions occurred in the past (follow-up 1982–2005). In another study of a copper smelter (Pope, Rodermund & Gee, 2007), a strike at the facility was associated with decreased mortality. However, the strike occurred in 1967/1968, after which emission standards were tightened. Emissions before tightening regulation from municipal waste incinerators were associated with non-Hodgkin’s lymphoma in France (Viel et al., 2008).

In a Canadian study with individual level confounder adjustment, living in the proximity of point sources was associated in small children with the development of asthma (Clark et al., 2010), but not with inflammation of the middle ear (MacIntyre et al., 2011). The category of “point sources” included all kinds of industrial facilities, from power plants and waste treatment facilities to shipyards, which limits the use of results to some extent. A study conducted in Texas reported a slightly increased risk for neural tube defects (Suarez et al., 2007), but not congenital heart defects (Langlois et al., 2009), around industrial point sources (petroleum refineries, primary metal or smelter facilities and the chemical industry).

Toxicological and clinical studies

No useful information could be identified to support the importance of industrial sources other than power plants and/or coal emissions. This is due largely to toxicological and

clinical studies having not been performed near sources of industrial emissions. In other words, the evidence is mainly derived from PM samples of which PM composition has been determined and used for source apportionment. For example, Steerenberg et al. (2006) identified, in a small data set, that industrial combustion and/or incinerators were associated with respiratory allergy. Specific data on the toxicity of industry emitted PM other than combustion-derived PM has not been published since 2005.

Biomass combustion

Epidemiological studies

The source category “biomass combustion” includes particles from residential wood combustion (also other types of solid fuels in developing countries), wildfires, and the burning of agricultural residues. In low-income countries, biomass is extensively used for heating and cooking, but it is most important as an indoor source, and the concentrations are substantially higher than outdoor concentrations in middle- and high-income countries. Long-term exposure to biomass PM from indoor use has been associated in low-income countries, for example, with lower respiratory infections (including pneumonia) in children, chronic obstructive pulmonary disease in women, and lung cancer. The 2005 global update of the WHO air quality guidelines concluded that there was little evidence that the toxicity of particles from biomass combustion would differ from the toxicity of more widely studied urban PM. However, there were at that time hardly any studies available on the cardiovascular or mortality effects of ambient biomass PM. In several European countries, high biomass burning contributions to ambient PM may be correlated with high levels of polycyclic aromatic hydrocarbons. Levoglucosan and potassium are very good tracers of biomass burning emissions; thus, these components can and will be used for epidemiological studies.

A systematic review of the health effects of particles from biomass combustion was published in 2007 (Naeher et al., 2007). The review concluded that there was no reason to consider PM from biomass combustion less harmful than particles from other urban sources, but that there were limited studies on the cardiovascular effects. However, most of the evidence on the effects of residential wood combustion was still indirect: studies were conducted in areas affected by wood combustion, but no specific indicators of wood combustion were available.

The few studies based on source apportionment (and published since 2005) provide an opportunity to compare the short-term health effects of particles from biomass combustion with particles from traffic – the source with the most evidence on health effects. In a study conducted in Copenhagen (Andersen et al., 2007), particles from biomass combustion were associated with cardiovascular and respiratory hospital admissions, whereas particles from traffic were not. In Atlanta, Georgia (Sarnat et al., 2008), woodsmoke was associated with cardiovascular emergency department visits as strongly as was traffic; neither of the sources was associated with respiratory health. In Phoenix, Arizona (Mar et al., 2006), wood combustion was associated with cardiovascular mortality, with effect estimates slightly lower than those for traffic particles. Finally, in Spokane, Washington (Schreuder et al., 2006), associations with cardiovascular mortality were of similar strength for biomass combustion and traffic. Only in a study conducted in Washington, DC (Ito et al., 2006), was no clear effect of particles from biomass combustion (or traffic) on cardiovascular health (mortality) observed. Altogether, these new studies suggest that cardiovascular effects of particles from biomass combustion may be comparable to those of traffic-related particles.

A recent study conducted in a woodsmoke impacted community provided evidence on the processes through which woodsmoke affects cardiovascular health (Allen et al., 2011). The introduction of portable air filters was associated with improved endothelial function and decreased inflammatory biomarkers; markers of oxidative stress were not affected. In another recent study, exposure to woodsmoke was associated with increased risk of physician visits for ear inflammation among children aged 1–24 months (MacIntyre et al., 2011). There are hardly any studies on the health effects of longer-term exposure to outdoor woodsmoke. In British Columbia, Canada, exposure to woodsmoke was associated with an increased risk of infant bronchiolitis, but not with the development of childhood asthma (Clark et al., 2010; Karr et al., 2009b). In California, PM_{2.5} from biomass combustion was associated with preterm birth, but not with low birth weight (Wu et al., 2011; Wilhelm et al., 2012).

Considering the effects of particles specifically from open biomass burning (wildfires and crop residue burning), there has been a lack of studies on cardiovascular health and mortality. In some studies published after a 2007 review (Naeher et al., 2007), no evidence of short-term cardiovascular effects was reported (Henderson et al., 2011; Morgan et al., 2010). However, one study reported associations between smoke from peat bog wildfires and congestive heart failure (Rappold et al., 2011), and another one reported associations between smoke from burning of sugar cane and hospital admissions for hypertension (Arbex et al., 2010).

Little evidence was found for an effect of wildfire smoke on mortality in the few published studies, since studies often lack statistical power. Significant cardiovascular effects during major forest fires have been reported, although it is not entirely clear what proportion of this could be attributed to exposure to PM (Analitis, Georgiadis & Katsouyanni, 2012). In contrast, evidence has continued to accumulate on the effects of wildfire smoke on respiratory health; in recent studies, not only total respiratory admissions and/or emergency department visits, but also visits due to chronic obstructive pulmonary disease, acute bronchitis, and pneumonia have been considered. Increased use of medication for chronic obstructive pulmonary disease and decreased lung function in schoolchildren have also been reported in association with exposure to PM from open biomass burning (Caamano-Isorna et al., 2011; Jacobson et al., 2012). A study conducted on forest fire-fighters associated exposure to high levels of woodsmoke with pulmonary and systemic inflammation, providing a potential link between exposure and both respiratory and cardiovascular diseases (Swiston et al., 2008). Interestingly, one recent study reported that exposure during pregnancy is associated with a slight decrease in birth weight (Holstius et al., 2012). It is not known, however, whether systemic inflammation mediates the effect.

Clinical and toxicological studies

Wegesser, Pinkerton & Last (2009) demonstrated that fine and coarse PM collected during wildfires are considerable more toxic in the mouse lung per unit mass than PM collected in the same area without fires. This was confirmed by Verma et al. (2009a), who tested PM collected during Los Angeles wildfires (see WHO Regional Office for Europe, 2012 – in which the effects have been summarized, with a focus on wood combustion). A more recent controlled human exposure study from Denmark reported that 3-hour exposure to woodsmoke with up to 354 µg/m³ of PM from a well-burning modern wood stove had no effect on markers of oxidative stress, DNA damage, cell adhesion, cytokines or microvascular function in atopic subjects, supporting the suggestion that burning conditions are dominant factors that determine the hazard of the combustion-derived particles. Another

Scandinavian study (Bølling et al., 2012) reported that the hazard of woodsmoke particles seems, to a large extent, to depend on the type of stove and combustion conditions (oxygen supply and water content). These outcomes suggest that a simple risk assessment for woodsmoke is not possible and the toxicity of the emitted PM can vary significantly. Notably, the toxicity seems to be clearly contingent on the organic fraction.

Desert dust

Epidemiological studies

After the 2005 global update of the WHO air quality guidelines, several new studies reported positive associations between short-term exposure to PM₁₀ or coarse particles and mortality during desert dust episodes (Chan & Ng, 2011; Jiménez et al., 2010; López-Villarrubia et al., 2012; Mallone et al., 2011; Perez et al., 2009a; Zauli Sajani et al., 2011; Tobías et al., 2011). However, PM₁₀ during desert dust episodes was not associated with either cardiovascular or respiratory mortality in Athens (Samoli et al., 2011b).

The results for cause-specific mortality have not been fully consistent for coarse particles: in Taipei, Taiwan, Province of China, coarse PM was associated with cardiovascular (and natural) mortality, but not with respiratory deaths (Chan & Ng, 2011), whereas in Rome both cardiovascular and respiratory mortality were affected. In most studies, PM₁₀ or coarse PM were more strongly associated with mortality during desert dust episodes than at other times (Jiménez et al., 2010; Mallone et al., 2011; Perez et al., 2009a; Tobías et al., 2011), but not in all studies (Zauli Sajani et al., 2011; Samoli et al., 2011b). For PM_{2.5}, no clear difference in effects between dust days and non-dust days has been observed (Mallone et al., 2011; Perez et al., 2009a; Tobías et al., 2011).

Only two recent studies have looked at the associations between desert dust days and hospital admissions. A study conducted in Hong Kong (Tam et al., 2012), reported an increased rate of hospitalization for chronic pulmonary disease, but not for pneumonia or influenza, during desert dust days. In contrast, in a study in Nicosia, Cyprus (Middleton et al., 2008), desert dust days were associated with an increased rate of hospitalization for cardiovascular, but not respiratory, causes. Saharan dust days in Barcelona, Spain, were found not to be associated with pregnancy complications (Dadvand et al., 2011).

Evidence for an effect of desert dust on human health is increasing, but at the moment it is not clear whether crustal, anthropogenic, or biological components of dust are most strongly associated with the effects. New results by Perez et al. (2012) found that during African dust outbreaks the PM fraction that shows better correlations with health outcomes is the non-African dust. Thus, it is possible that the health outcome of African dust outbreaks over Europe is related to specific components of anthropogenic PM that are enhanced during the outbreaks. A recent review stressed the importance of chemical characterization of desert dust (Karanasiou et al., 2012). The fraction of biological origin, however, remains largely unknown.

Toxicological studies

Only one study was identified that specifically investigated the adverse effects of an acute exposure to desert dust (Wilfong et al., 2011). Rats received a single dose in the lungs (1, 5, or 10 mg) of PM₁₀ collected in Kuwait. At 24 hours, 3 days, 7 days and 6 months, the effects on inflammation, cytotoxicity and pathology were very minimal compared with those of silica dust. Although the evidence is limited and obtained in healthy animals, the hazard per

gram associated with desert dust will most likely be smaller than that of, for example, combustion-derived PM or soluble transition metals. Of particular interest, Godleski et al. (2011) reported that viable pathogens in breathable dusts were identified in desert dust collected in Iraq and Kuwait, suggesting that the source is more complex in nature than sand. Polymenakou et al. (2008) found a large load of airborne microorganisms and pathogens during an intense African dust event in the eastern Mediterranean, and they concluded that the presence of aerosolized bacteria in small size particles may have significant implications for human health via intercontinental transportation of pathogens.

Ocean and sea

Epidemiological studies

Several short-term studies published since 2005 have included a source category for sea salt. With one exception, sea salt has not been associated with health outcomes (Andersen et al., 2007; de Hartog et al., 2009; Gent et al., 2009; Ito et al., 2006; Jacquemin et al., 2009; Lanki et al., 2006; Ostro et al., 2011; Penttinen et al., 2006). In a study by Mar et al. (2006), sea salt was associated with total and cardiovascular mortality. However, the effect was evident only 5 days after exposure, which suggests that chance may have a role in the finding. Recent studies that looked at the associations between individual components of PM and health did not find evidence of an effect for sodium, an indicator for sea salt. The exception is a study by Ito et al. (2011), which reported associations for cardiovascular mortality; however, no effect was observed for hospital admissions. On the other hand, Zanobetti et al. (2009) reported stronger effects of PM_{2.5} on cardiovascular hospital admission in areas with a high sodium content of particles. The authors suggested that the effect may be attributable to emissions from shipping. All in all, there is little epidemiological evidence of the harmfulness of sea salt.

Clinical studies

In Edinburgh, healthy and age-matched volunteers with stable coronary heart disease were exposed for 2 hours to PM_{2.5} ($190 \pm 37 \mu\text{g}/\text{m}^3$) and to clean filtered air using a randomized, double-blind crossover study design. After exposure to PM, there were increases in exhaled breath 8-isoprostane, in blood flow and in plasma tissue plasminogen activator ($P < 0.005$); but there were no significant changes in markers of systemic inflammation, and there was no effect on vascular function in either group of subjects (Mills et al., 2008). It was noted that most of the particulate mass consisted of sea salt, and far less PM was derived from combustion sources than was identified in the studies described above. The study provided clear evidence that PM dominated by sea salt and/or sea spray is far less toxic than equal amounts of combustion-derived PM.

Toxicological studies

In no study published since 2005 has the role of sea spray and/or sea salt been investigated, although sea salt is not classified as a hazardous compound and it is plausible that at current exposure levels no harmful effects will occur.

Hazardous waste sites

New studies have found little evidence of an effect of PM originating from hazardous waste sites on conotruncal heart defects or neural tube defects in offspring (Langlois et al., 2009; Suarez et al., 2007).

(c) The role of exposure times

Given that risk estimates of long-term exposure studies are usually much higher than those of short-term exposure studies, guidelines for yearly average concentrations will be of higher relevance than those based on 24-hour averages. It should also be noted that the EC's Second Position Paper on PM (2004) showed that, on a European scale, annual PM₁₀ averages and 90.4 percentile values of daily concentrations (equivalent to the daily limit value) of the corresponding year are highly correlated.

Both epidemiological and clinical studies have demonstrated that sub-daily exposures to elevated levels of PM can lead to adverse physiological changes in the respiratory and cardiovascular systems. This suggests that an averaging time of less than 24-hours – for example, 1 hour, similar to ozone – could be considered for air quality guidelines. However, the correlation between the 1-hour maximum and 24-hour average particle concentration is typically high. Furthermore, no studies have evaluated whether, for example, a high 1-hour exposure would lead to a different response than a similar dose given for 24 hours. The same is true for repeated very short-term exposures.

Epidemiological studies

Epidemiological studies published since the 2005 global update of the WHO air quality guidelines provide additional evidence on the effects of long-term (years) exposure to PM_{2.5} on morbidity and especially mortality (see Question A1). There is more limited evidence on the long-term health effects of PM₁₀, and mainly on respiratory outcomes (Question A4). Hardly any studies have evaluated the effects of long-term exposure to coarse particles, and none have evaluated them for ultrafine particles (see “(a) The role of other fractions or metrics of PM” in Question A2 above). For PM_{2.5}, there is also new evidence on the effects of (sub-yearly) exposure during pregnancy on adverse birth outcomes (Question A1).

Evidence has continued to accumulate on the associations of daily PM_{2.5} levels with both morbidity and mortality (Question A1). In addition, new epidemiological evidence links daily concentrations of coarse particles with increased respiratory and cardiovascular morbidity, and mortality (see “(a) The role of other fractions or metrics of PM” in Question A2 above). The evidence on the effects of 24-hour exposures to ultrafine particles on cardiorespiratory health is increasing, but is still limited.

Few epidemiological studies evaluate the health relevance of shorter than 24-hour exposures, and they focus mostly on cardiovascular health. Some recent population-based time-series studies have reported associations between hourly ambient PM concentrations and cardiovascular hospital admissions or mortality (Burgan et al., 2010). Unfortunately, in these studies the apparent effects of very short-term exposures are difficult to separate from the effects of 24-hour concentrations due to high correlation. There are also new panel studies that link very short-term changes in ambient PM (or in PM exposure measured with personal monitors) to adverse physiological effects. These studies suggest that physiological changes occur within hours of changes in PM exposure (Burgan et al., 2010; Delfino et al., 2010a; Ljungman et al., 2008; Schneider et al., 2010).

Interesting evidence comes from experimental studies that look at the health effects of traffic-generated air pollution: volunteers may have been asked to cycle, walk, or sit at a bus stop in the midst of busy traffic (Langrish et al., 2012; McCreanor et al., 2007; Weichenthal et al., 2011). The studies suggest that 1–2 hours of exposure may be enough to lead to harmful

physiological changes. In the most susceptible people, these changes might further lead to more serious exacerbations of chronic disease. The problem in these studies is that the effect of traffic-related PM is almost impossible to separate from the effects of gaseous pollutants and noise.

Susceptible population groups and effect mechanism differ for short-term and long-term exposures (Question A3). Even apparently healthy people are susceptible to the effects of long-term exposure to PM, because exposure can potentially accelerate progression of a disease, or perhaps even initiate it, until it is clinically diagnosed. Most susceptible to the effects of short-term exposures are those with an unstable disease. Progression of a disease due to particle exposure may be associated, for example, with acceleration of inflammatory processes, whereas other mechanisms may also play a role in triggering acute exacerbation of diseases, such as changes in autonomic nervous control of the heart in the case of cardiovascular diseases (Question A1; Brook et al., 2010). The fact that effect estimates in epidemiological studies are higher for long-term exposures than for short-term exposures demonstrates that long-term effects are not merely the sum of short-term effects.

Clinical and toxicological studies

Very little data has been published on health effects due to exposures to PM shorter than the usual 1–2-hour duration of clinical studies, whereas the pre-clinical studies have durations between a few hours and several months. In the study by Mills et al. (2007), patients with stable coronary heart disease have more ST-segment depression in their electrocardiogram tracings when exercising during exposure to diluted diesel exhaust ($300 \mu\text{g}/\text{m}^3$) than they do when exercising during exposure to clean filtered air. The effect of exposure on exercise induced ST-segment depression was highly consistent across patients and repeatable during sequential exercise periods. These findings were from a double blind randomized controlled trial, which would be considered strong evidence (Level 1). ST-segment depression is an important predictor of adverse cardiovascular events, but the magnitude of ST-segment depression in the trial was less than would be conventionally considered clinically significant. It is likely, however, that the magnitude of ST-segment depression would have been greater at higher workloads – trial patients were only asked to undertake gentle exercise in the exposure chamber. It should be mentioned that although exposure levels were high, they may occur in traffic hot spots of tunnels. Unfortunately, several variables – such as animal strain or species, and the type of test atmosphere – prevent statements to be made on the role of exposure times.

Question A3

EU legislation currently has a single limit value for exposure to PM_{2.5}, which is based on an annual averaging period. Based on the currently available health evidence, is there a need for additional limit values (or target values) for the protection of health from exposures over shorter periods of time?

Answer

Since the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006), when a 24-hour guideline for PM_{2.5} of 25 µg/m³ was set, the evidence for associations between 24-hour average exposures to PM_{2.5} and adverse effects on health has increased significantly. Thus, the 2005 global update of the WHO air quality guidelines support in establishing 24-hour limit values, in addition to an annual limit value, has been strengthened. Single- and multicity studies from the United States report associations between 24-hour average exposures to PM_{2.5} and both mortality and hospital admissions due to cardiorespiratory health problems. Because of the absence of monitoring PM_{2.5} in Europe until recently, the evidence from Europe is more limited; but where there are studies, the results are less consistent.

The following points need to be considered in legislative decisions.

1. Although short-term effects may contribute to chronic health problems, those affected by short-term exposures are not necessarily the same as those suffering from the consequences of long-term exposures.
2. Not all biological mechanisms relevant to acute effects are necessarily relevant to the long-term effects and vice versa.
3. In periods with high PM_{2.5} concentrations, health relevant action may be taken by citizens, public authorities and other constituencies.
4. Areas that have relatively moderate long-term average concentrations of PM_{2.5} may still have episodes of fairly high concentrations.

In light of the above considerations, the scientific evidence supports the health impacts and the need to regulate concentrations for both short-term averages (such as 24-hour averages) and annual means.

Rationale

Systematic monitoring of PM_{2.5} began in the United States in 1999 and more intermittently in Europe around 2009 – so prior to 2005, studies of its short-term impacts were limited. Since that time, several studies have documented associations between daily measurements of PM_{2.5} and both mortality and hospitalization. While the most comprehensive global assessment, which included European cities, was based on PM₁₀ (Katsouyanni et al., 2009) (highly correlated with PM_{2.5} in many cities), numerous studies are based on PM_{2.5} directly. For example, Ostro et al. (2006) analysed nine large counties in California and reported a 0.6% increase in mortality (95% CI: 0.2–1.0%) per 10 µg/m³ PM_{2.5}. Fine particles were also associated with cardiovascular and respiratory mortality, as well as with all-cause deaths for those above the age of 65 years. In a study of 25 cities in the United States., Franklin, Zeka &

Schwartz (2007) found an effect of 1.2% (95% CI: 0.3–2.1%) for a similar change in $PM_{2.5}$. Finally, in a study of 112 (for $PM_{2.5}$) and 47 (for PM_{10}) cities in the United States, Zanobetti et al. (2009) reported an effect of 1% (95% CI: 0.8–1.2%) for a $10 \mu\text{g}/\text{m}^3$ change in fine particles. A more complete review of both mortality and morbidity studies is provided by the EPA (2009). In Europe, there are only a few studies of $PM_{2.5}$ and mortality, and the results are less consistent. Among the positive studies, Ostro et al. (2011) and Perez et al. (2009a) reported the mortality effects of $PM_{2.5}$ in Barcelona (the latter study using $PM_{1.0}$). In addition, associations between fine particles and both all-cause mortality (during the warm season) and respiratory mortality and respiratory hospitalization were reported for various cities in the United Kingdom (Atkinson et al., 2010; Anderson et al., 2001). Finally, a study in Finland reported associations between daily exposures to $PM_{2.5}$ and increased cough in a panel of symptomatic children (Tiittanen et al., 1999). Other studies from Europe suggest fairly consistent associations between black smoke and both mortality and morbidity. A full review of these earlier studies of acute exposure can be found in Anderson et al. (2007).

While the United States studies have more consistent findings for cardiovascular outcomes, many studies also report associations of exposures to $PM_{2.5}$ with respiratory outcomes, including asthma, chronic obstructive pulmonary disease and respiratory infections. These studies encompass a wide range of underlying demographics, climates, co-pollutants and socioeconomic characteristics and are therefore believed to support causal associations between PM and adverse health. In addition, effects of 24-hour exposures are observed even in regions with relatively low annual averages of pollution, such as Canada (Burnett et al., 2004) and cleaner cities in the United States (Dominici et al., 2007b). For the most part, the effects are observed from 0 to 5 days after exposures and are greatly increased when cumulative (for example, 3- or 5-day moving averages) exposures are used as the exposure metric. While the risk per unit is much less than that observed for long-term (one year or more) exposure, the health costs resulting from short-term exposure to $PM_{2.5}$ are significant. For example, short-term changes in $PM_{2.5}$ levels lead to the early mortality of tens of thousands of individuals per year in the United States alone (Brook et al., 2010).

Although the effects of continued short-term exposure may contribute to the initiation or exacerbation of chronic disease, those affected by the acute exposures may reflect a distinct, susceptible subgroup with underlying or existing disease or unrecognized vulnerability. As such, this subgroup could be affected by single or repeated daily exposures to ambient PM concentrations that can exacerbate disease within hours or days. In contrast, long-term exposure is likely to contribute to the initiation and progression of underlying disease over months or years (Brook et al., 2010). Thus, short-term and long-term exposures can be considered to contribute to different stages of disease development within an individual or population subgroups at certain points in time.

Finally, even cities that have relatively low annual $PM_{2.5}$ averages can experience substantial variability in $PM_{2.5}$ throughout the year, with single or multiple day exposures that represent important public health burdens. This can occur seasonally or in multi-day episodes. The ratio of daily to annual average $PM_{2.5}$ can vary significantly by location and, in most cities, concentrations above those where daily impacts of $PM_{2.5}$ have been observed are likely to occur. These daily exposures will be particularly elevated in hot spot areas, such as near or in traffic or near stationary sources of $PM_{2.5}$. For example, high $PM_{2.5}$ exposures from transport were identified in studies in many cities in Europe and elsewhere (Zuurbier et al., 2010; Kaur, Nieuwenhuijsen & Colvile, 2007). Although these exposures typically have relatively short

durations, in-transport exposures have been shown to affect 24-hour personal exposure for $PM_{2.5}$ (van Roosbroeck et al., 2008; Brunekreef et al., 2005).

Therefore, to provide protection for all vulnerable subgroups, a limit value using a 24-hour average (in addition to an annual average) is warranted. Many countries and cities around the world issue pollution warnings when daily levels are considered at a hazardous level. This can motivate episode-specific control strategies, as well as inform the public, so that mitigation or coping decisions (such reducing driving, staying inside, reducing exercise, taking appropriate medications and seeing their doctors) can be taken. Thus, European citizens should have the right to know the daily $PM_{2.5}$ conditions and levels that are deemed to be hazardous. The establishment of a 24-hour limit guarantees the adoption of monitoring strategies that provide daily information. As an alternative, valid annual means can be established with monitoring strategies that do not provide daily air quality information.

Question A4

What health evidence is available to support an independent limit value for PM₁₀ (in parallel to (i) an annual average limit for PM_{2.5} and (ii) multiple limits to protect from short-term and long-term exposures to PM_{2.5})?

Answer

A sizable amount of scientific literature exists on the short-term and long-term health effects of PM₁₀ at concentrations below the current European limit values. The following arguments make it clear that PM₁₀ is not just a proxy measure of PM_{2.5}.

1. As reviewed above (Question A2), there is increasing evidence for the adverse effects on health of coarse particles (PM_{10-2.5}). Short-term effects on health of coarse particles have been observed independently of those related to fine particles (PM_{2.5}).
2. New European studies further strengthen the evidence for an association between long-term exposure to PM₁₀ and health – especially for respiratory outcomes – and for health benefits from the reduction in long-term mean concentrations of PM₁₀ to levels far below the current EU limit value for PM₁₀.
3. Coarse and fine particles deposit at different locations in the respiratory tract, have different sources and composition, act through partly different biological mechanisms, and result in different health outcomes.

Therefore, maintaining independent short-term and long-term limit values for ambient PM₁₀ in addition to PM_{2.5}, to protect against the health effects of both fine and coarse particles, is well supported.

Rationale

The 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) set long-term and short-term guideline values for PM₁₀ along with guideline values for PM_{2.5}. In 2007, a systematic review summarized the short-term health effects of PM (Anderson et al., 2007). The database on short-term health effects of PM₁₀ was the largest at the time and suggested associations between all cause-mortality, as well as hospital admissions from respiratory and cardiovascular diseases. Notable is the consistent evidence for the link between short-term changes in PM₁₀ concentrations and respiratory disease exacerbation that became apparent in the 2007 review.

Different deposition patterns of fine and coarse particle were documented (ICRP, 1994), with coarse particles having a higher deposition probability in the upper airways and the bronchial tree. Regional patterns of deposition are modified in children, and such respiratory diseases as chronic obstructive pulmonary disease and bronchitis produce uneven deposition patterns in the respiratory tract (Phalen, Mendez & Oldham, 2010). Particles deposited in the upper airways are cleared rather rapidly from the respiratory tract, as long as such clearance mechanisms as mucociliary clearance and macrophage transport are not hampered by underlying diseases (Geiser & Kreyling, 2010). Therefore, coarse particles may induce health effects by different mechanisms than fine and ultrafine particles and potentially relate to different health outcomes.

As reviewed for Question A2, there is scientific evidence for independent short-term effects of coarse particles, based on the EPA (2009) integrated science assessment for PM. In light of the evidence on deposition patterns in the respiratory tract and the potential for rapid clearance of the micron-size particles, the short-term health effects of PM₁₀ and coarse PM seem plausible. The review of the evidence on the short-term health effects of coarse particles and tyre and brake wear particles (in Question A2) also identified a potential link to cardiovascular disease exacerbation. One of the plausible links could be provided by the activation of the autonomous nervous system via irritant receptors in the upper airways (Brook et al., 2010; Peters et al., 2006).

As reviewed in Question A2, there is very limited evidence of long-term health effects of coarse particles available to date. No systematic assessment of studies on long-term health effects of PM₁₀ in Europe is available. However, a query at the annotated database on health effects of air pollution maintained at the Swiss Tropical Public Health Institute identified 75 studies that reported on long-term health effects of PM₁₀ from Europe since 2005. Overall, the ability to separate long-term health effects of PM₁₀ from other pollutants, such as NO₂ or PM_{2.5}, was limited and the evidence mixed. Nevertheless, an association between long-term exposure to PM₁₀ and mortality in women cannot be ruled out. Gehring et al. (2006) found an increased risk of cardiopulmonary disease mortality in elderly women associated with PM₁₀ (relative risk (RR): 1.34 (95% CI: 1.06–1.71) per 7 µg/m³). This association with PM₁₀ was independent of an association with traffic indicators in two exposure models. For the Nurses' Health Study, Puett et al. (2009) showed independent associations of PM_{2.5} and coarse particles (though weaker) with total mortality. However, no association was observed using similar approaches in men for either PM_{2.5} or coarse particles (Puett et al., 2011).

The SAPALDIA study (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults) found stronger declines in lung function associated with high levels of modelled PM₁₀ concentrations at the homes of 4742 adults, compared with low levels of PM₁₀ (Downs et al., 2007). No other measures of air pollution were available. The Children's Health Study made similar observations in children, but assessed PM_{2.5} and elemental carbon (Gauderman et al., 2004). Consistent with the decline in lung function, more frequent respiratory symptoms were reported in Swiss adults in association with PM₁₀ (Schindler et al., 2009). Cross-sectional data from 12 European countries on children, (based on nearly 50 000 children) showed an association between respiratory symptoms and PM₁₀, but not lung function (Hoek et al., 2012). While a meta-analysis of long-term exposure to PM₁₀ and asthma prevalence showed no association, a potential link to asthma incidence cannot be ruled out (Anderson, Favara & Atkinson, 2013a,b). Furthermore, a recently published study on 481 adults with asthma suggested asthma severity is associated with PM₁₀ (Jacquemin et al., 2012).

A number of studies have indicated that PM₁₀ exposure during pregnancy, in addition to NO₂ exposure, is able to impact pregnant women and neonates. Heterogeneous results were observed when comparing 14 studies that assessed exposure to pollution during pregnancy and birth weight (Parker et al., 2011). The Generation R Study showed increases in blood pressures for more than 7000 pregnant women, in association with both PM₁₀ and NO₂ (van den Hooven et al., 2011), and further indicated an impact on adverse birth outcomes during a subsequent study (van den Hooven et al., 2012a). A small study of 241 children suggested an association between PM₁₀ during pregnancy and lung function in 5-week-old children (Latzin et al., 2009), as was shown earlier for active and passive smoking. Unfortunately, these studies do not allow a distinction to be made between PM₁₀ and PM_{10-2.5}.

There is a moderate to strong correlation between PM_{10} and $PM_{2.5}$ on a spatial scale in Europe, as documented by the European Study of Cohorts for Air Pollution Effects (ESCAPE) study, with correlations ranging between 0.62 (Oslo, Stockholm, Vorarlberg) to 0.86 (Greater London, Rome) (Eeftens et al., 2012b). Furthermore, the ESCAPE study showed that, for long-term exposure, $PM_{2.5}$ and coarse PM may not be highly correlated across the different regions of Europe, as correlations ranged between 0.02 (Vorarlberg) and 0.81 (Paris). The ESCAPE study showed that, for all seasons, the highest concentrations were observed in dry climates. Coarse particles in European urban areas often consist of re-suspended road particles that contain a mixture of soil, tyre wear and brake wear, as well as particles that can be transported regionally from desert areas (Eeftens et al., 2012b). Thereby, the ESCAPE study substantiated earlier reports that indicated that PM_{10} and $PM_{2.5}$ are independent when considering a wide range of European measurement sites (Putaud et al., 2010).

Based on the evidence reviewed above, a clear picture emerges that coarse particles are an independent entity distinct from fine and ultrafine particles. Sufficient evidence exists for proposing a short-term standard for PM_{10} , to protect against the short-term health effects of coarse particles, in addition to fine particles. Alternatively, a short-term exposure limit value for coarse particles ($PM_{10-PM_{2.5}}$) may be considered and could be regarded as adequate for protecting against coarse particles, provided that an effective $PM_{2.5}$ short-term exposure limit is enacted. A limit to protect against long-term exposure should be maintained as new evidence is published on health effects of long-term exposure to PM_{10} from Europe and as long as there remains uncertainty about if these health effects would be eliminated by reducing long-term exposure to $PM_{2.5}$ alone. This concern exists especially for respiratory and pregnancy outcomes, while cardiovascular disease and other diseases related to systemic inflammatory responses are more likely to be linked to long-term exposures to fine particles.

Question A5

EU legislation has a concentration limit value and an exposure reduction target for PM_{2.5}. To decide whether it would be more effective to protect human health through exposure reduction targets rather than limit or target values it is important to understand (among other things, such as exposure, cost-effectiveness, technical feasibility) the shape of the concentration-response functions. What is the latest evidence on thresholds and linearity for PM_{2.5}?

Answer

The existence of a threshold and the linearity of the relationship between exposure to PM_{2.5} and health response have been the subject of several studies published since 2005. The power to assess these issues is particularly strong for studies of short-term effects. Studies of long-term exposure face greater methodological challenges to fully assess thresholds and linearity.

- **Thresholds.** For studies of short-term exposure, there is substantial evidence on associations observed down to very low levels of PM_{2.5}. The data clearly suggest the absence of a threshold below which no one would be affected. Likewise long-term studies give no evidence of a threshold. Some recent studies have reported effects on mortality at concentrations below an annual average of 10 µg/m³.
- **Linearity.** The European studies of short-term exposure that have rigorously examined concentration-response functions have not detected significant deviations from linearity for ambient levels of PM_{2.5} observed in Europe. Few long-term studies have examined the shape of the concentration-response functions. There are, however, suggestions of a steeper exposure-response relationship at lower levels (supra-linear) from analyses of studies from different areas around the globe and with different ranges and sources of exposure.

In the absence of a threshold and in light of linear or supra-linear risk functions, public health benefits will result from any reduction in PM_{2.5} concentrations, whether or not the current levels are above or below the limit values.

Rationale

Researchers have evaluated the shape of the concentration-response function using a variety of approaches, including such non-parametric functions as (penalized) splines (Schwartz et al., 2008). These functions do not assume a fixed shape, as in linear regression. Key issues were the evaluation of the presence of a threshold below which no effect can be detected and the levelling off of the concentration-response curve at high concentrations. The assessment of the shape of the response function often addresses both, the deviation of linearity and the potential existence of a threshold of no effect. In epidemiological studies, the presence of a threshold is evaluated at the population level and is affected by the wide range of individual responses. The absence of thresholds at the population level does not imply the nonexistence of thresholds at the individual level. Actually, the latter are heavily determined by susceptibility factors that may vary between individuals, as well as within a subject over time. Studies have evaluated whether the concentration-response functions deviate significantly

from linear functions and have typically found no evidence for this. Studies have generally not evaluated whether other functions provide an even better fit.

For *short-term exposure*, studies that have assessed the shape of the concentration–response function have found no evidence of a threshold for the effects of PM_{2.5} (United States) and PM₁₀ (Europe and the United States) on mortality, despite many observations being below current standards. Many of these (often multicity) studies were published before the 2005 global update of the WHO air quality guidelines, but there is now supporting information from new multicity studies (Dominici et al., 2007a; Katsouyanni et al., 2009; Samoli et al., 2005). Within the multicity European APHEA (Air Pollution and Health: a European Approach) study (Samoli et al., 2005), a linear function represented the concentration–response function well across the range (up to a daily average concentration of 200 µg/m³). Fewer studies have assessed the shape of the association for morbidity effects. A recent study in Madrid found no evidence of a threshold and a linear association between PM_{2.5} and hospital admissions for respiratory and cardiovascular disease (Linares & Díaz, 2010).

For *long-term exposure*, evidence has increased substantially in the past years that associations are present with little evidence of a threshold. Prior to 2005, analyses within the American Cancer Society study found no evidence of a threshold (Pope et al., 2002). Novel insights were provided through the extended follow-up of the Harvard Six Cities Study, which indicated that, with decreasing air pollution concentrations over the past decades, the air quality had improved substantially over the Eastern United States, but the estimated PM_{2.5} effects on mortality had remained consistent and displayed exposure–response relationships below the United States standard of 15 µg/m³ (Schwartz et al., 2008; Lepeule et al., 2012). Associations were found down to 8 µg/m³ in the last follow-up (Lepeule et al., 2012). In addition, a recent large Canadian study (published in 2012) of very low PM_{2.5} concentrations showed strong evidence for an exposure–response relationship between PM_{2.5} at or below current standards and all-cause and cardiovascular disease mortality (Crouse et al., 2012). Because of the sizable fraction of long-term average exposures below 10 µg/m³, a more robust assessment of the shape of the association with cardiovascular and natural cause mortality at these low levels was possible.

Further support for the absence of a threshold was found in an analysis of life expectancy and PM_{2.5} across the United States (Pope, Ezzati & Dockery, 2009). The study reported a larger increase in life expectancy in areas with a larger decrease in PM_{2.5} between 1980 and 2000. However, the PM_{2.5} concentrations in 2000 were still associated cross-sectionally with lower life expectancy, indicating that additional public health gains can be obtained with further reductions of PM_{2.5}.

A study comparing effects of outdoor particles, particles from second-hand smoke and active smoking found no evidence of a threshold for lung cancer and cardiovascular mortality (Pope et al., 2011). A linear dose–response function was found for lung cancer, but the dose–response function was much steeper at low doses (outdoor particles and second-hand smoke) than at high doses for cardiovascular mortality (Pope et al., 2011). It is uncertain whether this assessment, based on comparing outdoor air pollution and particles from smoking, will apply to high outdoor concentrations as well, given differences in particle composition.

In the extended analysis of the American Cancer Society study, the logarithm of PM_{2.5} represented mortality risks for all outcomes slightly better than the linear function (Krewski et al., 2009). The logarithmic function predicted higher risks at low concentrations than the

linear model. The RR for all-cause mortality per $10 \mu\text{g}/\text{m}^3$ was 1.08 (95% CI: 1.04–1.12) for the linear model and 1.13 (95% CI: 1.08–1.18) for a change from $5 \mu\text{g}/\text{m}^3$ to $15 \mu\text{g}/\text{m}^3$ and 1.08 (1.05–1.11) for a change from $10 \mu\text{g}/\text{m}^3$ to $20 \mu\text{g}/\text{m}^3$ for the logarithmic model (Krewski et al., 2009).

The implication of the Pope, Ezzati & Dockery (2009) study and other studies on outdoor particles is that, within Europe, it is reasonable to use linear concentration–response functions to assess risks. Linear functions may overestimate risk gradients in areas with high air pollution concentrations – for example major cities and rapidly developing mega-cities with very high air pollution concentrations.

More powerful analyses in the framework of the project on the global burden of disease are now challenging the issue of linearity further with more sophisticated methods (Lim et al., 2012). These findings point as well to no-threshold response functions possibly being supra-linear, in the sense of observing somewhat larger effects in the lowest range of ambient concentrations – such as those relevant for the EU countries – and smaller effects for a given change in exposure in areas with high levels of pollution (such as Asian mega-cities). For EU Member States, this would mean that the benefit of cleaner air would be underestimated if linearity was assumed.

Question A6

Based on currently available health evidence, what PM metrics, health outcomes and concentration–response functions can be used for health impact assessment?

Answer

The evidence base supports quantification of the effects of several PM metrics and both short-term and long-term exposures (see Questions A1, A3 and A4). Specifically, a large body of evidence from cohort studies exists to support quantification of the effects of long-term exposure to PM_{2.5} on both mortality (all-cause and cardiovascular) and morbidity. In addition, studies of short-term exposure support quantification of the acute effects of PM_{2.5} on several morbidity outcomes.

There are other PM metrics for which response functions have been published for at least some health outcomes, including PM₁₀, the coarse fraction of PM₁₀, black carbon, sulfate and others. Its use depends on the purpose of the health impact assessment. Health impact assessors could employ black carbon, as an indicator primarily for traffic-related PM, using published short-term or long-term response functions. However, compared with PM_{2.5}, there are fewer studies and/or fewer health outcomes available for black carbon and other alternative metrics. Risk assessments based on PM_{2.5} studies will be the most inclusive. Alternative metrics, such as black carbon, may be used in sensitivity analyses. One needs to keep in mind that the impact derived for different PM metrics should not be summed up, given that the effects and sources are not fully independent.

Details of the health impact assessment methods are discussed further in the HRAPIE project (Question D5). We highlight only the following general issues.

- There are many recently conducted and published health impact assessments for different PM metrics and averaging times that can serve as a basis for the quantification, including the recent update of the project on the global burden of disease. These health impact assessments draw from epidemiological studies conducted in both Europe and North America.
- In selecting pollutant-outcome pairs for a health impact assessment, the availability of related health data needs to be taken into account in framing the health impact assessment, as the lack of data may be a limiting factor.
- Mortality data for all natural causes tend to be more reliable than cause-specific mortalities. On the other hand, air pollution is not related to all causes of death; thus, cause-specific assessments are more defensible. In light of such methodological conflicts, both analyses may be done to elucidate the sensitivity of results in their application to the EU population.
- For morbidity, baseline data are not necessarily available for every Member State and, therefore, may need to be estimated or derived from local studies or from other countries.
- Given the breadth of the existing evidence and the uncertainty inherent in health impact assessments, the sensitivity of results (due to making different assumptions) needs to be communicated.

Rationale

Since the 2005 global update of the WHO air quality guidelines, many new studies have provided useful information to support the use of functions applied to previous health impact assessments and have also provided additional health outcomes and concentration–response functions (see Questions A1 and A3 for reviews of new studies). For health impact assessments, one needs information about several factors, including: (a) the risk function (concentration–response function), which relates concentrations to risks of death or disease; (b) the pollution concentrations for the exposed population that is the target of the health impact assessment; and (c) the baseline frequency of the health outcome used in the health impact assessment.

With regard to concentration–response functions, the richest set of studies provides quantitative information for PM_{2.5}, but many studies would also provide concentration–response functions for PM₁₀ (or coarse particles, specifically), and a recent review provides concentration–response functions for black carbon. For ultrafine particle numbers, no general risk functions have been published yet, and there are far fewer studies available. Therefore, at this time, a health impact assessment for ultrafine particles is not recommended. Some risk assessments are based on newly developed methods that use *proximity to major roads* as a possible marker of those near-road pollutants, but it is not clear how to generalize *proximity* in European-wide health impact assessments and to what degree it captures ultrafine particles.

With regard to ambient concentrations, the availability and quality of information about the various fractions differ with the measurements or models available for PM_{2.5} or PM₁₀. Much fewer data are available to estimate the population exposure distribution for black carbon. Also, exposure assessment for ultrafine particles is very difficult, given its spatial heterogeneity.

Baseline frequency of health outcomes is available for mortality and a subset of the possible morbidity end-points. However, it is possible that reasonable assumptions can be made for other morbidity end-points.

The primary focus of the health impact assessment will be PM_{2.5}. Alternatively, one could consider PM₁₀, but one cannot simply sum up the impact associated with each, due to substantial overlap. However, it may be possible to at least add the effects of short-term exposures to coarse particles to the PM_{2.5} estimates, especially in areas where the correlations between the two are modest ($r < 0.3$). Similarly, adding black carbon health impact assessments to the PM_{2.5} health impact assessments may not be appropriate, as one cannot claim complete independence of the two. However, comparing the impact of PM_{2.5} with the one based on black carbon may be considered in a sensitivity analysis. For black carbon, a concentration–response function has been published for the mortality effects of long-term exposure (Smith KR et al., 2009). When possible, the estimates for PM_{2.5} should use studies that control for the impact of other pollutants, such as ozone and NO₂, when there is a possibility of double counting.

A single-pollutant model is preferred if it has been shown that the PM_{2.5} effect is robust to adjustment for other pollutants. As an alternative, estimates for the multipollutant model can be used or considered for a sensitivity analysis. If a single pollutant model is used, it should be indicated that the effects may be due to covarying pollutants, either measured or

unmeasured. If the original epidemiological study suggests that an effect is possibly *shared* by more than one pollutant, but the health impact assessment attributes the effect to a single pollutant, it should be carefully documented as such. In addition, if the correlations among the pollutants are high ($r > 0.6$), it may be preferable to use the estimate from a single pollutant model.

With regard to the health outcomes to be included, we recommend considering at least those used in published health impact assessments. In case a cost–benefit analysis or an economic valuation of current pollution effects is envisioned, the assessment of the impact related to mortality should be given priority and should include years of life lost, as those strongly dominate the health estimates. The following mortality and morbidity outcomes are the primary candidates for inclusion in the health impact assessment, given that they have been used in previous health impact assessments.

Mortality outcome:

1. premature attributable death (all causes) due to acute (for example, one or more days) exposures, all ages, giving preference to the distributed lag concentration–response functions, when available;
2. attributable death (all causes or cardiovascular or cardiopulmonary and lung cancer) associated with long-term exposure (concentration–response functions from long-term studies) for adults older than 30 years, with the possibility of subclasses of cardiovascular disease, such as ischaemic heart disease, being estimated separately;
3. years of life lost in association with long-term exposure of adults older than 30 years; and
4. attributable cases of infant mortality (0–1 year of age).

The distributed lag concentration–response function, mentioned in item 1, captures the impact of multiple days of exposure and therefore provides more accurate estimates of the effects relative to concentration–response functions based on a single day of exposure.

In case of adult deaths, it is useful to present both the acute and the long-term cases although the former is, at least, partly contained in the latter.

Morbidity outcome:

1. bronchitis symptoms in children under the age of 18 years;
2. chronic bronchitis in adults older than 30 years;
3. asthma attacks, all ages;
4. cardiovascular, cerebrovascular (possibly) and respiratory hospital admissions, all ages;
5. urgent care visits due to asthma (and possible other respiratory outcomes) and cardiovascular disease, all ages; and
6. restricted activity days, adults.

While some of these morbidity outcomes will be difficult to estimate, given the lack of baseline incidence rates, reasonable assumptions can be formulated. While the total economic impact of the morbidity outcomes will be small relative to those of mortality, quantitative estimates will provide important information about the impact of air pollution to both policy-makers and the public at large. Such information is an important aspect of any health impact

assessment. Therefore, while estimates for restricted activity days are based on fairly old studies, they should be considered for inclusion, to reflect their economic impact on the work force.

The final selection of metrics, outcomes and functions will require an interdisciplinary team and experts in the field of health impact assessment. As a starting point, adopting previously published methods may be appropriate, given the new evidence does not contradict, but rather complements, the evidence that was used to guide previous health impact assessments. We recommend, in particular, that the team review the methods used in Clean Air for Europe (CAFE) and other projects, such as that on the global burden of disease. For the 2002 report on the global burden of disease, quantitative estimates of the effects of outdoor air pollution were based on four concentration–response functions: (1) adult cardiopulmonary mortality from long-term exposure to PM_{2.5}; (2) adult lung cancer mortality from long-term exposure to PM_{2.5}; (3) acute respiratory infection mortality for children under age 5, due to short-term exposure to PM₁₀; and (4) all-age all-cause mortality associated with short-term exposure to PM₁₀ (Cohen et al., 2005). A European expert panel determined that the study generating the most important impact – mortality from long-term exposure to PM_{2.5}, which is based on data from the United States – could be extrapolated to populations in other geographic regions (Cooke et al., 2007). Since this effort, dozens of additional health impact assessments have been published that include several additional end-points. The recent Global Burden of Disease Study 2010 provides an update and indicates that several new concentration–response functions are available and that additional scientific support is provided for the outcomes estimated previously. This effort has undergone and successfully passed significant peer review, and new worldwide impacts are currently being calculated. The analysis draws on the expertise of more than two dozen international experts and therefore serves as an appropriate basis for addressing this issue. The updated analysis, which focuses on PM_{2.5}, provides additional support for quantitative concentration-response functions for cardiopulmonary mortality and lung cancer in adults, and acute respiratory infections for infants. The methods and many of the findings were published in *The Lancet* and other peer-reviewed journals (Lim et al., 2012; Burnett et al., under review).

Since the report on the global burden of disease provides worldwide estimates and since there are significant differences in baseline rates of specific diseases in some countries relative to the countries from which the concentration–response functions were derived (primarily the United States, Canada and Europe), the current analysis of the global burden of disease uses more specific disease end-points, such as ischaemic heart disease, stroke and chronic obstructive pulmonary disease. However, for the impact assessment of Europe, broader categories (such as cardiovascular, cardiopulmonary or even all-cause mortality) can be used, since baseline health conditions in Europe are fairly similar to those in the United States. These mortality estimates can be supplemented by estimates of nonfatal incidences of several diseases. In addition, recent efforts generated by the EPA’s Environmental Benefits Mapping and Analysis (BENMAP) program provide support for additional outcomes. These and the associated concentration–response functions were chosen based on several criteria, including use of appropriate exposure metrics, study design and location, characteristics of the study population, and generalizability of the study to other locations. Ultimately, the studies used were similar to those used in recent EPA regulatory analyses, which underwent significant peer review before being issued. For example, Fann et al. (2012) generated estimates for premature mortality in adults from: long-term exposure, infant mortality, chronic bronchitis, nonfatal heart attacks, hospital admissions for both cardiovascular and respiratory disease, emergency room visits for asthma, acute bronchitis, lower and upper respiratory symptoms,

asthma exacerbations, lost work days, and restricted activity days. Population life years lost from long-term exposure can also be estimated. Forthcoming results from the ESCAPE studies may provide supportive evidence of effects of long-term exposure to PM_{2.5} and can be integrated with the existing studies.

The health impact assessment can also draw from several recent assessments of PM_{2.5} in Europe. The health impact assessment and cost–benefit analysis for the Clean Air for Europe (CAFE) Programme is a good starting point, summarized in the WHO Regional Office for Europe & Convention on Long-range Transboundary Air Pollution (CLRTAP) Task Force on the Health Aspects of Air Pollution report on the health risks of PM from transboundary air pollution (2006: Chapter 7), and with more detail in Hurley et al. (2005). The CAFE Programme included concentration–response functions for most of the health outcomes described above, using metrics for PM_{2.5} (where available), or else for PM₁₀, with a focus on studies in Europe (where available). For some health outcomes, the background rates were estimated from very sparse data and should, if possible, be improved or discontinued. The Air Pollution and Health – a European Information System (APHEIS) project used a limited set of concentration–response functions – that is, mortality from long-term exposure and hospital admissions from short-term exposure, but with detailed work on background rates in the cities selected (Medina, Le Tertre & Saklad, 2009). Concentration–response functions for mortality from long-term exposure were later reviewed by the United Kingdom’s Committee on the Medical Effects of Air Pollutants (COMEAP, 2009a) and, subsequently, also by the Health and Environment Integrated Methodology and Toolbox for Scenario Assessment (HEIMTSA) project and discussed by the Task Force for Health of CLRTAP. These all-cause estimates may be superseded by the cause-specific recommendations on the global burden of disease noted above. Other work in Europe has focused on how impacts from long-term exposure can be expressed in terms of population survival (life years), deaths and life expectancy at birth – see COMEAP (2010). The latter COMEAP report also recommends that estimates in changes of life expectancy are preferred to annual deaths. Among morbidity outcomes in CAFE (2005), the greatest impact was given by attributable new cases of chronic bronchitis, using concentration–response functions from the United States Seventh-day Adventist Study. More recently the HEIMTSA project proposed using Schindler et al. (2009) as a European basis for quantifying the same outcome.

Although a more careful review will be necessary to determine precisely which end-points and concentration–response functions should be used in any updated health impact assessment for Europe, the studies and methods cited above provide ample evidence for developing estimates for a wide range of health outcomes. The precise methodology for the health impact assessment will depend on the data available for Europe. However, a focus of the health impact assessment should be to estimate the health benefits of moving from current ambient levels to both the WHO guidelines and the levels in EU Directive 2008/50/EC. Relevant sensitivity analyses should be included as well. In light of the lack of a no-effect threshold, one may include rural background levels as a reference point, as well give the full range of possible benefits of clean air policies.

Finally, the interdisciplinary team may attempt to expand upon previous health impact assessments, with an attempt to develop methods and tools to integrate new evidence of effects of PM_{2.5}, such as its impact on birth outcomes. The inclusion of long-term effects on the incidence of childhood asthma could be part of such extensions, given the evidence of near-road air pollution’s contribution to the development of asthma in childhood and its substantial economic burden on entire families. Other chronic morbidities may be considered

as well and methods developed to integrate the indirect burden of morbidity related to the effects of pollutants on preclinical functional measures, such as lung function or artery wall thickness, and neurodevelopment and other emerging outcomes associated with PM_{2.5}. If a new case of a chronic disease occurs due to long-term exposure to PM_{2.5}, the entire future *disease career* – that is, the sum of all exacerbations, complications and limitations in quality of life – could to be taken into account.

B. Health effects of ozone

Question B1

What new evidence on health effects has emerged since the review work done for the 2005 global update of the WHO air quality guidelines, particularly with regard to the strength of the evidence on the health impacts associated with short-term and long-term exposure to ozone?

Answer

The 2005 global update of the WHO air quality guidelines found support only for short-term effects of ozone on mortality and respiratory morbidity.

- Since 2005, several cohort analyses have been published on long-term ozone exposure and mortality. There is evidence from the most powerful study, by the American Cancer Society, for an effect of long-term exposure to ozone on respiratory and cardiorespiratory mortality, which for the latter is less conclusive. Also, there is some evidence from other cohorts for an effect on mortality among people with potentially predisposing conditions (chronic obstructive pulmonary disease, diabetes, congestive heart failure and myocardial infarction).
- Additionally, several new follow-up long-term exposure studies have reported adverse effects on asthma incidence, asthma severity, hospital care for asthma and lung function growth.
- New evidence published since 2005 on adverse effects from short-term exposure to ozone comes from large, multicentre time-series studies in Europe, the United States and Asia. In Europe, adverse effects of short-term exposure to daily concentrations of ozone (maximum 1-hour or 8-hour mean) on all-cause, cardiovascular and respiratory mortality have been reported. Adverse effects of exposure to daily ozone concentrations on both respiratory and cardiovascular hospital admissions, after adjustment for the effects of particles (PM₁₀), have also been reported.
- In the 2005 review, toxicological data from animal and human exposure studies already provided ample support for the short-term effects of ozone on a range of pulmonary and vascular health-relevant end-points. The evidence has strengthened in the intervening period. In addition, new findings from a range of experimental animal models, including primates, provides evidence of chronic injury and long-term structural changes of the airway in animals exposed for prolonged periods to ozone and to ozone and allergens combined.
- New epidemiological and experimental data, for both human beings and animal models, suggest an effect of ozone exposure on cognitive development and reproductive health, including preterm birth.

Rationale

The correlations between ozone and other harmful air pollutants differ by season and place, making confounding control complicated. During summer, there is often a positive

correlation with secondary particles, since similar conditions increase the formation of both. On the other hand, especially when ozone formation is limited (winter), there are often strong inverse correlations between ozone and primary pollutants from traffic and heating, because nitric oxide emissions scavenge ozone (Lee et al., 2003; Lipfert et al., 2006). Thus, the apparent absence of adverse effects of ozone in winter may become similar to summer results after adjustment for the concentration of primary pollutants that may act as confounders (Gryparis et al., 2004). These factors suggest that, for health impact assessments, consideration be given to the use of concentration–response functions *adjusted* for such co-pollutants as PM.

A further complexity in the study of the health effects of ground level ozone, particularly the health effects associated with short-term exposures, arises from the close correlation between ozone production and depletion with meteorological conditions (Royal Society, 2008). Since high temperatures (Baccini et al., 2008) and heat waves in particular (Kovats & Hajat, 2008) are associated with increased mortality, the separation of the health effects of ozone from those of temperature is problematic. Studies of short-term exposure to ozone, such as time-series studies, include temperature terms in their statistical models, to estimate an independent effect of ozone. A small number of studies have specifically set out to explore how temperature modifies the short-term effects of ozone on mortality (Ren et al., 2008b).

Here we focus our attention on outcomes for which appropriate denominator data – data on populations that is independent of any disease or condition – are available for health impact assessment calculations.

Epidemiological studies of long-term exposure

Long-term ozone exposure and mortality

The 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) found support only for a short-term effect of ozone on mortality. No statistically significant association between long-term exposure and mortality was observed in a study from California, the Loma Linda University Adventist Health and Smog (AHSMOG) study (Abbey et al., 1999), while a subset analysis of the United States Veterans study found an effect of peak ozone (95th percentile of daily mean) (Lipfert et al., 2006). In the large American Cancer Society cohort study, there was no indication of an association between ozone and all-cause or cause-specific mortality when ozone was represented by the mean of the daily 1-hour maximum, 1980–1981, but when more exposure data were used (covering more years), a positive association was indicated (Pope et al., 2002). With ozone data from the summers 1982–1998, the association with cardiopulmonary mortality ozone was borderline significant.

Since 2005, several cohort analyses (Table 1) have been published; together they suggest an effect of long-term exposure to ozone on mortality, at least for respiratory or cardiorespiratory mortality, especially in people with potential predisposing conditions (Lipfert et al., 2006; Krewski et al., 2009; Jerrett et al., 2009a; Smith KR et al., 2009; Zanobetti & Schwartz, 2011). Generally, these studies do not include ozone exposure from cohort entry to death, and some use limited monitoring data.

In the large American Cancer Society cohort study extended follow-up, summer ozone levels had a significant association with total and, especially, cardiopulmonary mortality (Krewski et al., 2009). However, in this *between-city analysis*, the high correlation between PM_{2.5} and

ozone makes it difficult to separate the effects of the two pollutants. In a further study, the correlation between ozone and PM_{2.5} resulted in unstable risk estimates for both pollutants and cardiopulmonary, cardiovascular and all-cause mortality, with only respiratory mortality being significantly associated with ozone after adjustment for PM_{2.5} (Jerrett et al., 2009a).

In the cohort study of United States male veterans, only ozone (peak ozone) was significant in combination with traffic density, and it was only weakly correlated with PM_{2.5} (Lipfert et al., 2006).

Most studies have controlled for important potential confounders and co-pollutants. Smith KR et al. (2009) used the American Cancer Society cohort study and controlled for both sulfate and elemental carbon; they found a significant association with cardiopulmonary mortality in the three-pollutant model. A test for interaction suggested that ozone effects were stronger where sulfate levels were low. Less than 10% of the deaths were due to respiratory causes, and less than 20% were cardiopulmonary deaths. Thus, it seems unlikely that only respiratory deaths are driving the association.

Jerret et al. (2009a) and Smith KR et al. (2009) both used data from the American Cancer Society cohort study and daily 1-hour maximum ozone, with both papers presenting air pollution effects adjusted for a large number of covariates. The paper by Jerrett et al. reports ozone results adjusted for PM_{2.5}, whereas the study by Smith KR et al. reports ozone results with simultaneous adjustment for two different constituents of PM_{2.5}: elemental carbon and sulfate. In the study by Jerret et al., the two-pollutant models for all-cause mortality, cardiopulmonary mortality and cardiovascular mortality show statistically significant, negative associations between ozone and mortality. Given the many known adverse effects of ozone, such protective effects are very unlikely and may reflect problems with the model specification in this study.

To eliminate potential confounding by factors that vary across cities, Zanobetti & Schwartz (2011) studied year-to-year variations in 8-hour mean daily ozone concentrations around the long-term trend in relation to variations in mortality around the mortality trend. Their study focused on cohorts of potentially vulnerable individuals and was limited to the months of May through September. More recently, analysis of the same Medicare cohort as in their earlier study, Zanobetti et al. (2012) assessed ozone and temperature effects during the same years (1985–2006) in 135 cities. Again, significant effects of ozone were found in the four cohorts of people with chronic disease.

Table 1. Cohort studies of long-term ozone exposure and mortality^a

Cohort	Outcome/exposure	Main results	Comments	Reference
United States veterans About 7 500– 11 500 deaths 1989–1996 and/or 2001	Total mortality RR from Cox model using peak ozone: 95th percentile of daily 1- hour maximum, county level from monitoring stations	RR for peak ozone: 1.13 for 40 ppb in multiple pollution models	RR for peak ozone (similar to earlier study) (Lipfert et al. (2000)) Weaker effect in a sub-analysis of counties with NO ₂ data 1997–2001	Lipfert et al. (2006)
WHI study 65 893 women without previous CVD 36 United States metropolitan areas	No analysis of ozone and mortality, only to first CVD event	Ozone not significant	--	Miller et al. (2007)

Cohort	Outcome/exposure	Main results	Comments	Reference
American Cancer Society CPS-II cohort extended follow-up 118 777 deaths 9891 from respiratory causes 96 metropolitan areas	Total and cause-specific mortality (cardiopulmonary, cardiovascular, respiratory). RR from Cox model Average of 2 nd -3 rd quarters daily maximum 1-hour ozone from all EPA AIRS monitors (1–57) in each study area, 1977–2000	In two-pollutant models with PM _{2.5} , only the association with respiratory mortality remained significant; RR: 1.040 per 10 ppb (95% CI: 1.013–1.067).	A high correlation between ozone and PM _{2.5} resulted in unstable risk estimates for both pollutants. Ozone gave significant reduction of total mortality in model with PM _{2.5} .	Jerrett et al. (2009a)
American Cancer Society CPS II cohort extended follow-up 352 242 participants 66 metropolitan study areas	Total and cardiopulmonary mortality. RR from Cox model, ozone measurements from April to September, refers to Krewski et al. (2009) for details. However, IQR 22 µg/m ³ shows that daily 1-hour maximum was used as in Jerret et al. (2009).	Cardiopulmonary mortality increased 0.09% per 1 µg/m ³ (95% CI: 0.01–0.17%) in a three-pollutant model.	Weaker association with total mortality	Smith KR et al. (2009)
Medicare data used to construct cohorts of people hospitalized with chronic conditions	All-cause mortality. Cox model included year-to-year variations in May to September mean daily 8-hour around the city-specific long-term trend	HR: 1.06 (95% CI: 1.03–1.08) per 5-ppb increase in summer average ozone for people with congestive heart failure HR: 1.09 (95% CI: 1.06–1.12) for myocardial infarction. HR: 1.07 (95% CI: 1.04–1.09) for COPD. HR: 1.07 (95% CI: 1.05–1.10) for diabetics.	No adjustment for year-to-year variations in particle levels.	Zanobetti & Schwartz (2011)
American Cancer Society CPS-II cohort extended follow-up 118 metropolitan study areas (ozone study)	Total and cause-specific mortality. RR from Cox model. 1980 annual and summer (April to September) mean ozone from AIRS averaged for each metropolitan study area. (A sub-analysis for metropolitan Los Angeles used the 4 highest 8-hour means from 2000).	HR (in the nationwide study): 1.02 (95% CI: 1.01–1.03) per 10 ppb summertime ozone for all-cause mortality HR: 1.03 (95% CI: 1.02–1.04) for cardiopulmonary mortality in single pollution models.	1980 annual ozone levels gave no significant associations.	Krewski et al. (2009)

Cohort	Outcome/exposure	Main results	Comments	Reference
California Teachers Study (a prospective cohort of female public school professionals) 100 000 participants	Total and cause-specific mortality RR from Cox model Annual and 3 rd quarter concentrations from neighbourhood monitors.	Only HR for IHD mortality and summer ozone was significant; HR: 1.09 for 23 ppb (95% CI: 1.01–1.19).	Positive associations with IHD mortality disappeared in two-pollutant models with PM.	Lipsett et al. (2011)

AIRS: Aerometric Information Retrieval System; COPD: chronic obstructive pulmonary disease; CPS: Cancer Prevention Study; CVD: cardiovascular disease; HR: hazard ratio; IHD: ischaemic heart disease; WHI: Women's Health Initiative.
1 ppb = 2 µg/m³
^a Published after 2005.

Long-term ozone exposure and respiratory morbidity

Before 2005, there was limited support for chronic effects of ozone on respiratory health. A recent systematic review of outdoor air pollution and asthma in children concluded that chronic exposure to ambient ozone may increase the risk of asthma hospital admission among children (Tzivian, 2011). The paper by Tzivian reviewed studies published 2006–2009, and with its inclusion criteria (a full version available in PubMed) found 12 prospective studies.

One systematic review of lung-function effects included studies of long-term ozone exposure, but did not present a meta-analysis (Götschi et al., 2008), and the results presented for lung-function were rather inconsistent.

A conference report on the evidence of health effects of ozone by McClellan et al. (2009) did not discuss new evidence from long-term studies of ozone and respiratory morbidity.

The EPA Second External Review Draft of *Integrated science assessment of ozone and related photochemical oxidants*, Chapter 7 (entitled “Integrated health effects of long-term exposure”), focuses on the evaluation of evidence from studies presented after the review in the 2006 ozone air quality criteria document. It concluded that the strongest epidemiological evidence for a relationship between long-term ozone exposure and respiratory morbidity is provided by new studies that demonstrate associations between long-term measures of ozone exposure and new-onset asthma in children and increased respiratory symptom effects in asthmatics (EPA, 2012). The California multi-community prospective cohort studies reviewed in the EPA report are seen as methodologically rigorous epidemiological studies in this regard (Islam et al., 2008, 2009; Salam, Islam & Gilliland, 2008).

Recent systematic meta-analyses of multi-community asthma prevalence studies (Anderson, Favarato & Atkinson, 2013a) found no effect of ozone on asthma prevalence. A review of cohort studies to examine asthma incidence (Anderson, Favarato & Atkinson, 2013b) found too few studies of ozone and incidence for a quantitative meta-analysis to be performed. The recent California studies were not included in the Anderson meta-analysis because they focused on associations among genetic subgroups and used categorical exposure indicators (high/low).

However, since 2005, several studies have been published on ozone and new-onset asthma, asthma severity and control, and hospital care for asthma.

Some of the new studies of respiratory morbidity are more important, due to their good design and/or large size; and some are more important because, in the context of the current review exercise, they are from Europe:

A large, prospective cohort study of non-asthmatic children 8 years old (at inclusion) in Mexico City ($n = 3170$) analysed the association between long-term exposure to ozone and lung function growth, assessed every 6 months from April 1996 through May 1999 (Rojas-Martinez et al., 2007). Also, in multipollutant models that incorporate a number of pollutants, the 6-month mean of the daily maximum 8-hour ozone concentration was associated with deficits in lung function growth.

Lin et al. (2008) followed a birth cohort born in New York State during the period 1995–1999 from first asthma admission or until 31 December 2000. Asthma admissions were associated significantly with all three indicators of chronic ozone exposure (mean concentration, summer mean and % days with ozone levels greater than 35 ppb.¹

The relationship between measures of lung function (forced expiratory volume in 1 second (FEV1) and FEV1 as a percentage of forced vital capacity (FVC)) and long-term exposure was examined in four representative cross-sectional surveys of the English population aged 16 years in 1995, 1996, 1997 and 2001 (Forbes et al., 2009). Year-specific estimates were pooled, using fixed effect meta-analysis. For ozone, there was no indication of an adverse effect.

In a cross-sectional analysis of immunoglobulin E (IgE) levels among 369 asthmatic adults from the French Epidemiological study on Genetics and Environment of Asthma (EGEA), geo-statistical models were performed on 4 x 4 km grids to assess individual outdoor air pollution exposure (Rage et al., 2009). The annual mean and summer mean concentrations of ozone were associated with IgE, indicating that exposure to ozone may increase total IgE in adult asthmatics.

In a later paper from the EGEA study, asthma control was assessed in 481 subjects with current asthma (Jacquemin et al., 2012). After controlling for sex, age, body mass index, education, smoking and use of inhaled corticosteroids, three domains of asthma control (symptoms, exacerbations and lung function) were assessed. The results suggest that long-term exposure to ozone is associated with uncontrolled asthma in adults, defined by symptoms, exacerbations and lung function.

Long-term exposure and other outcomes

The amount of evidence for effects on birth outcome has also increased; in particular, ozone has been associated with an increase in preterm birth in several new studies (Jiang et al., 2007; Jalaludin et al., 2007; Olsson, Ekström & Forsberg, 2012; Lee P et al., 2013, Olsson, Mogren & Forsberg, 2013) and with an increase in cognitive decline (Chen & Schwartz, 2009). Preterm birth is not a health effect itself, but an important predictor of health. These findings will probably motivate further studies in coming years.

Epidemiological studies of short-term exposure

¹ 1 ppb = 2 µg/m³

Using the St George's, University of London systematic review programme Air Pollution Epidemiology Database (APED), we identified 95 time-series studies that provided effect estimates for ozone indexed in Medline, Embase or Web of Knowledge between 2006 and April 2011 (Table 2). Thirty-six studies reported results for mortality from a range of causes and 46 reported results for hospital admissions. The majority of the remaining studies considered emergency room and/or department visits. Since 2005, the majority of the evidence has come from studies in the Americas and Europe. However, there has been a substantial increase in the number of studies of ozone and mortality conducted in Asia (corresponding to WHO Western Pacific Regions A and B). Prior to 2006, the Asian literature represented 19% (19 of 102) of worldwide mortality studies. This proportion increased to 39% (14 of 36 studies) after 2005. A similar increase was found for studies of hospital admissions in Asia, up from 20% (17 of 85 studies) before 2005 to 48% (22 of 46 studies) after 2005. Only a single study (of admissions) published results from South-East Asia (WHO South-East Asia Region). Details of the WHO regions are available from the WHO website (WHO, 2013).

Table 2. Number of studies recording effect estimates from time-series studies

Category and year published		WHO Region						Total	
		AFR	AMR	EMR	EUR	SEAR	WPR		Multi
Mortality	Total ≤ 2005	--	47	--	35	--	19	1	102
	Total > 2005	--	7	--	13	--	14	2	36
	SC	--	2	--	6	--	13	--	21
	MC	--	5	--	7	--	1	2	15
Admissions	Total ≤ 2005	--	40	--	26	--	17	2	85
	Total > 2005	--	9	--	14	1	22	--	46
	SC	--	6	--	9	1	22	--	38
	MC	--	3	--	5	--	--	--	8

WHO regions: AFR: Africa; AMR: Americas; EMR: Eastern Mediterranean; EUR: Europe; SEAR: South-East Asia; WPR: Western Pacific; Multi:-more than one WHO region.
SC: single city; MC: multiple cities.

The most informative evidence published since 2005 on the health effects of short-term exposure to ozone on mortality and morbidity comes from two recent, large, multicentre studies: the APHENA (Air pollution and health: a European and North American approach) study (Katsouyanni, 2009) and the PAPA (Public Health and Air Pollution in Asia) study (HEI, 2010, 2011). The APHENA study combined data from 12 cities in Canada, 90 in the United States and 32 in Europe. A standard analytical protocol was applied in all locations prior to pooling their respective findings. The APHENA study reported associations for the 1-hour ozone metric. The PAPA study also applied a standard analytical protocol, as well as standardized data collection, in its study of six large Asian cities (Bangkok, Hong Kong Special Administrative Region, Shanghai, Wuhan, Chennai and Delhi). The PAPA study reported associations for the 8-hour mean (10:00–18:00) ozone metric. Together, these two multicentre studies also reflect the geographical distribution of new evidence published since 2005. Other recent European multicity studies include studies in England & Wales (Pattenden et al., 2010), France (Lefranc et al., 2009), Italy (Stafoggia et al., 2010) and Spain (Ballester et al., 2006).

The second draft of the EPA’s integrated science assessment (EPA, 2012) reviewed the published time-series evidence for cardiovascular and respiratory mortality from 2006 to 2011 and also focused on results from the APHENA study. Other reviews include the quantitative systematic review of the literature conducted by St George’s, University of London for the United Kingdom Department of Health, using data in the peer-reviewed literature indexed up to January 2006 (Anderson et al., 2007). A more recent meta-analysis of ozone associations was provided by Smith, Xu & Switzer (2009). A review of the Asian time-series literature also includes associations between ozone and mortality published up to May 2009 (Atkinson et al., 2010).

Associations between ozone and hospital admissions were analysed in the APHENA project. In the United States, hospital admissions were obtained from the Medicare system; in Europe, data were available from 8 cities; and in Canada from 12 cities. Hospital admissions were stratified by cause (respiratory and cardiovascular) for subjects more than 65 years of age. Hospital admissions were not analysed in the PAPA study. Other sources of information on short-term associations between ozone and hospital admissions were: a systematic review and meta-analysis of respiratory hospital admissions (Ji, Cohan & Bell, 2011); a review of associations between ozone and cardiovascular disease (COMEAP, 2006) (although the evidence reviewed was published prior to 2003); the systematic review and meta-analysis for the United Kingdom Department of Health (Anderson et al., 2007) (including evidence from studies indexed in the peer-reviewed literature up until 2006); and a review of the Asian literature (Atkinson et al., 2010).

Table 3 summarizes the findings for European cities from the APHENA study for all-cause and cause-specific mortality and cardiovascular and respiratory admissions. In Europe, positive associations were observed in the all-year analyses for 1-hour ozone and all-cause mortality, cardiovascular and respiratory mortality – associations that persist after adjustment for PM (PM₁₀). Estimates of all effects had lower CI above zero, with the exception of respiratory mortality. Seasonally stratified (summer or winter) results for both 1-hour and maximum 8-hour ozone and mortality, using the same data set, were published by Gryparis et al. (2004) – results for 8- and 1-hour metrics were similar. For hospital admissions, positive associations were observed between 1-hour ozone and respiratory and cardiovascular disease after adjustment for PM₁₀ only. The positive associations with cardiovascular admissions were not observed in cities in the United States in the APHENA study or in earlier reviews (COMEAP, 2006; Anderson et al., 2007).

Table 3. Associations between short-term exposure to ozone and mortality and hospital admissions in European cities in the APHENA study

Outcome	Per cent increase in deaths/admissions (95% CI) per 10 µg/m ³ increment in daily maximum 1-hour ozone concentrations	
	Single pollutant	Adjusted for PM ₁₀
All-cause mortality ^a	0.18 (0.07–0.30)	0.21 (0.10–0.31)
Cardiovascular mortality: 75 years and older ^a	0.22 (0.00–0.45)	0.21 (-0.01–0.43)
Cardiovascular mortality: younger than 75 years ^a	0.35 (0.12–0.58)	0.36 (0.10–0.62)
Respiratory mortality ^b	0.19 (-0.06–0.45)	0.21 (-0.08–0.50)
Cardiac admissions: older than	-0.10 (-0.46–0.27)	0.64 (0.36–0.91)

65 years ^a		
Respiratory admissions: older than 65 years ^b	0.19 (-0.28–0.67)	0.32 (0.05–0.60)

^a lag 0-1 results; ^b lag 1 results.

Note. Results for models using penalized splines with 8 degrees of freedom per year are reported.

Table 4 presents results for respiratory admissions from two recent meta-analyses of the literature. It provides coefficients for health impact assessments for specific age groups and respiratory diseases. Summary estimates from Ji, Cohan & Bell (2011) provide coefficients for health impact assessments, for hospital admissions and for respiratory diseases in all age groups and in adults – results not available from the APHENA study – and for chronic obstructive pulmonary disease (all ages) and asthma admissions (children, adults and all ages combined). All associations were positive, though not all had lower CI above zero.

Table 4. Associations between ozone and respiratory hospital admissions

Study	Location	Age range (years)	Disease	Estimated % increase in admissions (95% CI) ^a (number of estimates)
Atkinson et al. (2012a) ^b	Asian cities	All	Respiratory	0.26 (-0.06, 0.59) (4)
Ji, Cohan & Bell (2011) ^c	Worldwide	All	Respiratory	0.62 (0.24, 1.00) (10)
		Elderly	Respiratory	1.45 (0.80, 2.11) (11)
		Adults (15–64)	Respiratory	0.35 (-0.43, 1.13) (6)
		All	COPD	1.65 (0.41, 2.91) (6)
		All	Asthma	2.15 (0.85, 3.48) (8)
		Children	Asthma	0.95 (-1.13, 3.06) (6)
:		Adults (15–64)	Asthma	1.23 (-0.71, 3.24) (6)

COPD: chronic obstructive pulmonary disease^c

^a Per 10 µg/m³ increment in maximum 8-hour daily ozone concentrations.

^b Review period 1980–2007; 8-hour ozone per 10 µg/m³.

^c Review period 1990–2008; English language only; 8-hour ozone estimates scaled to per 10 µg/m³ from per 10 ppb.

Experimental and panel studies

One of the key advantages of human exposure challenges is that the exposure is defined and relevant end-points can be examined in detail. They avoid the complication of extrapolating findings from animal and in vitro model exposures where concentrations far outside the ambient range are often employed to examine underlying biological mechanisms. Their results, however, need to be interpreted with caution, when aligned with short- and long-term health effects reported from epidemiological studies. By definition, they address only a sole pollutant in the majority of circumstances, but this can be helpful when it's unclear whether the health effects reported in the real world are related to the actual pollutant or to a mixture of pollutants for which it acts as a tracer. For ozone, clear and extensive literature demonstrates its toxic potency, which has been well reviewed since 2005 (Stanek et al., 2011a; second draft of the EPA's integrated science assessment: EPA, 2012), though there remains the question of whether considering ozone alone underestimates the toxicity associated with the complete photochemical mixture. This point is addressed in the Answer to Question B4.

Human clinical studies generally examine healthy subjects or relevant patient groups with stable symptoms who have been exposed to a single ozone concentration for durations between 1 and 6 hours. The results are generally compared with a control air exposure, with a range of end-points examined, including lung function, exhaled gases, airway inflammation (either by bronchoscopy, but more recently, especially within the United States, by induced sputum) and airway hyperresponsiveness. Studies have also examined vascular and cardiovascular responses under controlled chamber conditions. The results observed from these acute exposures are usually transient and though often statistically significant are seldom clinically so. Much of the early ozone literature focused on lung function decrements immediately after exposure, but there is now an acknowledgement, voiced by the American Thoracic Society (ATS, 2000), that for these results to be viewed as “adverse”, they need to be associated with other adverse responses, such as the presence of inflammation, cell death or tissue remodelling. The question of what can be considered an adverse response is central to interpreting the results from human exposure studies. Generally, small but statistically significant transient responses in healthy controls are viewed as important baselines against which to consider the likely responses in sensitive subpopulations, which might be expected to be larger. This view is not wholly supported by the literature.

An extensive volume of literature examines the induction of transient decrements in lung function in healthy young human subjects, usually non-smokers, exposed to ozone for a broad range of concentrations (40–600 ppb), with exercise for periods up to 8 hours under controlled conditions. This literature has been reviewed previously (McDonnell, Stewart & Smith, 2007; EPA, 2012). Since the 2005 global update of the WHO air quality guidelines, a considerable effort has been invested in attempting to produce predictive models that describe the relationship between lung function decrements (FEV1) and inhaled ozone dose, to assess risk and identify response thresholds (McDonnell, Stewart & Smith, 2007, 2010; McDonnell et al., 2012; Schelegle et al., 2009). Schelegle et al. (2009) exposed healthy young adults to varying concentrations of ozone (60, 70, 80 and 87 ppb) for 6.6 hours, with continuous exercise ($V_E = 40$ litres per minute), and reported significant decrements at 70 ppb, but not 60 ppb. Recent studies have tended to support evidence of small, but measureable, decrements at 60 ppb (Brown, Bateson & McDonnell, 2008; Kim et al., 2011). More detailed modelling studies have provided evidence of thresholds for these transient lung function responses. McDonnell et al. (2012) employed data from 23 controlled human exposures, consisting of lung function measurements from 741 subjects, and found that the best fit non-linear model included a threshold assumption. Using this expanded data set, compared with their previous analysis (McDonnell, Stewart & Smith, 2010), thresholds were identified to be equivalent to “moderate, near continuous exercise for 1 h to 0.06 and 0.08 ppm ozone and for 2 h to 0.04 ppm, and those at rest for 1 h to 0.18 and 0.24 ppm ozone and for 2 h to 0.12 ppm”. A separate analysis by Schelegle et al. (2012) using a smaller but overlapping data set also supported a threshold model, based on the assumption that responses only occur once inhaled ozone has overcome endogenous antioxidant defences, inducing oxidative stress in the lung.

It should be noted that acute lung function decrements have also been reported in populations with high outdoor exposures to ozone (children attending summer camps, exercising adults and outdoor workers in moderate to high ozone communities) at concentrations lower than those observed in chamber studies (Kinney, Thurston & Raizenne, 1996; Brunekreef et al., 1994; Thaller et al., 2008; Chan & Wu, 2005). In the reanalysis of the children’s summer camp study by Kinney, Thurston & Raizenne (1996), which included data from 616 children, a 40 ppb increase in hourly ozone concentrations was associated with a 20 ml decrease in afternoon FEV1. This relationship was not confirmed in a later Belgian study of children

attending summer camps, despite ambient hourly maximum ozone concentrations being in an equivalent range to the Kinney, Thurston & Raizenne (1996) study, 24–110 ppb (1-hour maximal concentrations) (Nickmilder et al., 2007).

A further cardinal feature of the acute response of the human airway to ozone is the induction of inflammation – particularly, neutrophil recruitment into the lung. A meta-analysis of human bronchoscopy-based studies (Mudway & Kelly, 2004) demonstrated a linear relationship between airway neutrophilia and inhaled dose (defined as a function of ozone concentration, exposure duration and subject ventilation rate), implying a threshold above that observed at the time for the transient decrements in lung function. Subsequent to this analysis, studies employing induced sputum to sample the upper and central airways have demonstrated inflammation following prolonged exposures to 80 ppb (Alexis et al., 2010) and 60 ppb ozone (Kim et al., 2011). Airway inflammation has also been examined in a number of panel studies, using exhaled nitric oxide as a non-invasive measure of allergic inflammation. While there appears to be a clear relationship between ozone and health effects in children (Liu et al., 2009; Berhane et al., 2011; Nickmilder et al., 2007; Barraza-Villarreal et al., 2008; Siembra-Monge et al., 2004), the data for adults is mixed (Delfino et al., 2010b; Eiswerth, Douglass Shaw & Yen, 2005). There is little evidence from panel studies to demonstrate this association is stronger in asthmatic children (Berhane et al., 2011; Barraza-Villarreal et al., 2008). The issue of the basis for the reported heightened sensitivity of asthmatics remains unresolved (Hernandez et al., 2010; Stenfors et al., 2010), as does the benefit of vitamin supplementation, despite evidence that ozone elicits oxidative stress in the lung (Tashakkor, Chow & Carlsten, 2011; Gomes et al., 2011).

Since 2005, there have been a number of key experimental animal studies carried out in mice that demonstrated acute inflammation and airway injury following acute (Damera et al., 2010) or sub-chronic exposure (Inoue et al., 2008; Yoon, Cho & Kleeberger, 2007) to environmentally pertinent ozone concentrations in the range 100–300 ppb. Additional sub-chronic and chronic ozone exposure studies (500 ppb) in rhesus monkeys have demonstrated structural changes in the distal and proximal airways (Fanucchi et al., 2006; Carey et al., 2011) and allergy-like patterns of response (increased goblet cells and eosinophils) to allergen and ozone co-challenges (Kajekar et al., 2007; Miller et al., 2009; van Winkle et al., 2010; Plopper et al., 2007). These studies would therefore seem to support the epidemiological observations that reported impaired lung growth (peak flow: Gauderman et al., 2002; FVC and FEV1: Rojas-Martinez et al., 2007) and a worsening of asthma symptoms in children with high ozone exposures (asthma incidence: McConnell et al., 2002; Islam et al., 2009; asthma medication usage: Millstein et al., 2004).

Despite experimental support for cardiovascular effects of ozone (such as vascular oxidative stress and/or inflammation, increased heart rate, increased diastolic pressure, decreased heart rate variability and decreased nitric oxide bioavailability, for 2-hour to multi-day exposures to 500–800 ppb ozone) from animal models (Chuang et al., 2009; Perepu et al., 2010; Tankersley et al., 2010), results from controlled human studies remain ambiguous (Kusha et al., 2012; Fakhri et al., 2009). Similarly, investigation of blood biomarkers (reflecting haemostasis and inflammation) of cardiovascular risk in panel studies have provided inconsistent associations with ozone, complicated by the different averaging times and lag structures examined (Rudez et al., 2009; Thompson et al., 2010; Chuang et al., 2007; Liao et al., 2005; Steinvil et al. 2008).

Also an increasing amount of data supports impaired cognitive function in populations exposed to ozone, which is consistent with the animal toxicological literature. Using the Third National Health and Nutrition Examination Survey (NHANES III) cohort, an association between annual ozone exposure and decreased cognitive function and short-term memory was observed in the adult population (Chen & Schwartz, 2009). Memory impairment was also observed in rats exposed to ozone acutely – exposure for 4 hours to 400–1000 ppb (Dorado-Martínez et al., 2001; Rivas-Arancibia et al., 2000; Avila-Costa et al., 1999) – and sub-chronically, 250 ppb for 15–90 days, 4 hours a day (Rivas-Arancibia et al., 2010). Exposure to ozone has also been associated with oxidative injury to various brain regions in the rat, including the striatum, substantia nigra, cerebellum, olfactory bulb, frontal and prefrontal cortex, either through acute high dose exposures (1 ppm for 4 hours: Rivas-Arancibia et al., 2000), or longer duration low dose challenges (7–60 day exposure to 250 ppb ozone for 4 hours a day: Rivas-Arancibia et al., 2010; Martínez-Canabal et al., 2008; Mokoena et al., 2010; Guevara-Guzmán et al., 2009).

Prior to 2005, there was some limited, if somewhat contradictory, evidence supporting an adverse effect of ozone on prenatal development (Kavlock, Daston & Grabowski, 1979; Kavlock, Meyer & Grabowski, 1980; Bignami et al., 1994). Kavlock, Daston & Grabowski (1979) demonstrated that fetal reabsorption increased following exposure to high ozone concentrations, 1.26 ppm ozone during mid-gestation, with a later study (Kavlock, Meyer & Grabowski, 1980) demonstrating reduced weight gain in the offspring. More recent studies have reported a diverse range of prenatal effects following maternal ozone exposure of rats and mice, including adverse fetal lung development (1 ppm, 12 hours for 18, 20 or 21 days of gestation: López et al., 2008), neurotransmitter deficiencies (1 ppm for the entire pregnancy: Gonzalez-Pina et al., 2008), and increased lung injury and impaired immune function in offspring following 10 days of exposure to 1.2 ppm for 4 hours a day (Sharkhuu et al., 2011). Evidence has also emerged that suggests that exposure to elevated ambient ozone concentrations has an effect on sperm count and quality in human beings (Rubes et al., 2005; Sokol et al., 2006; Hansen et al., 2010), an observation partially collaborated in a chronic ozone exposure study (500 ppb ozone, 5 hours a day for 50 days) in rats (Jedlińska-Krakowska et al., 2006).

Question B2

What new health evidence has been published in relation to the evidence or likelihood of a threshold below which impacts are not expected?

Answer

Epidemiological studies reporting an effect of long-term exposure to ozone on mortality do not, in general, provide data that permit the firm identification of a threshold for the effects of long-term exposure to ozone.

Recent experimental exposures of healthy human volunteers to ozone at concentrations of $120 \mu\text{g}/\text{m}^3$ (60 ppb) have shown impaired lung function and inflammation, relative to clean air controls, but thus far only in healthy young adults exposed for prolonged periods (6.6 hours), with exercise. These conditions are unlikely to reflect fully the range of exposures experienced in the general population and the real world combinations of susceptibility and exposure. The effects of ozone on lung function and inflammation have been reported for real world situations, most notably in summer camp studies at lower concentrations, less than $110 \mu\text{g}/\text{m}^3$ (55 ppb), as an 8-hour average. It has been argued that the responses at these lower levels may be due to subpopulations with greater susceptibilities or to additional effects of other stressors, such as other pollutants. The evidence from epidemiological studies for a threshold for short-term exposure is inconsistent with some large, multicity studies that reported little evidence of a threshold down to near background ozone concentrations, whereas other short-term studies suggest a threshold between $20 \mu\text{g}/\text{m}^3$ and $90 \mu\text{g}/\text{m}^3$ (10 ppb and 45 ppb) (daily maximum 1-hour). In summary, the evidence for a threshold for short-term exposure is not consistent, but where a threshold is observed, it is likely to lie below $90 \mu\text{g}/\text{m}^3$ (45 ppb) (maximum 1 hour).

Rationale

Epidemiological studies of long-term exposure

The studies that suggest that long-term exposure has an effect on mortality do not in general provide data to examine the support for a threshold. For respiratory mortality, there was limited evidence that a threshold model improved model fit (Jerrett et al., 2009a). In several studies of long-term exposure, mean concentrations for summer months or peak ozone seem to give stronger associations (Lipfert et al., 2006; Krewski et al., 2009), possibly indicating that the highest exposure levels are important.

Epidemiological studies of short-term exposure

A small number of time-series studies have specifically considered the threshold issue (Hoek et al., 1997; Kim et al., 2004; Gryparis et al., 2004; Ito, De Leon & Lippmann, 2005; Bell, Peng & Dominici, 2006). A variety of methodological approaches have been used. The most comprehensive analysis was carried out by Bell & Dominici (2008) using data from 98 urban communities in the United States for the period 1987–2000. They investigated the concentration–response function for ozone and mortality using a variety of methods, including: (a) a linear approach; (b) a subset approach (limiting the analyses to days with ozone concentrations below a predetermined value only); (c) a so-called hockey stick threshold model (assuming the regression coefficient is 0 below the hypothesized threshold

value and non-zero above the threshold value); and (d) a spline approach, in which the relationship between ozone and mortality is described using a non-linear function of ozone. The authors found robust evidence of a linear relationship between ozone exposure and mortality, even when they used data that included only 24-hour ozone levels nearing background concentrations (typically from 10 ppb to 25 ppb). They concluded that "... any anthropogenic contribution to ambient ozone, however slight, still presents an increased risk for premature mortality" and "Interventions to further reduce ozone pollution would benefit public health, even in regions that meet current regulatory standards and guidelines". Both Kim S et al. (2004) and Hoek et al. (1997) used subsets of these methods to arrive at similar conclusions.

Additional evidence was sought by searching the citation list for the Bell, Peng & Dominici 2006 paper. Of the 142 papers citing this article (checked 30 May 2012), 3 reported findings on evidence for a threshold in the concentration–response relationship. Stylianou & Nicolich (2009) analysed data from nine cities in the United States National Morbidity, Mortality and Air Pollution Study (NMMAPS) and reached a different conclusion from that of Bell, Peng & Dominici (2006): "Many models exhibited thresholds (10–45 ppb)" and that the assumption of linearity "was not appropriate". Similarly, Pattenden et al. (2010) also reported evidence for a threshold (at 33 ppb, using daily maximum 8-hour ozone) in their study of mortality in 15 British conurbations. A recent study by Powell, Lee & Bowman (2012) analysed daily mean ozone and respiratory mortality data for London and concluded that there was clear evidence for a threshold near 50 $\mu\text{g}/\text{m}^3$. This was also the conclusion from a recent analysis of London data (daily 8-hour ozone), although the evidence from other urban and rural areas in England and Wales was less conclusive (Atkinson et al., 2012b).

The APHEA-2 project studied the relationship between maximum 8-hour mean ozone and mortality stratified by season (Gryparis et al., 2004). Without adjustment for PM_{10} , there was little evidence for an association in the winter months. Upon adjustment for PM_{10} , the linear associations were comparable. The concentration–response relationship for all-cause mortality was studied in the summer months only and was consistent with a linear relationship (the lowest median concentrations of 8-hour ozone were in London, at 41 $\mu\text{g}/\text{m}^3$). The APHENA study investigated the evidence for a threshold in the ozone–(1-hour) mortality concentration–response function in Europe, using the same data set as in the APHEA-2 project. It utilized threshold models, testing a range of threshold values, and concluded that "the pollutant-mortality association is essentially linear"; however, it was cautious about this conclusion stating that "with small effects typical of these studies, limited power existed to detect thresholds".

Experimental studies

Exposure–response relationships are available for the impact of ozone inhalation on indices of lung function. These were available and reviewed in the 2005 global update of the WHO air quality guidelines. These studies highlight the importance of considering inhaled total dose, as opposed to focusing on the headline ozone concentration employed (McDonnell, Stewart & Smith, 2007). They also demonstrate the relatively greater influence of subject ventilation rate, over the duration of exposure. Recent studies have tended to support evidence of small, but measureable, decrements in lung function at and below 60 ppb (Brown, Bateson & McDonnell, 2008), as well as potential thresholds near the current European air quality standard (McDonnell et al., 2012; Schelegle et al., 2012). A detailed review of these studies is provided in the Rationale for Question B1. The literature examining the basis for these acute changes in lung capacity has expanded during the last five years,

particularly with regard to the capacity of ozone and ozone oxidation products in the lung to stimulate transient receptor potential (TRP) subfamily A member 1 channels on vagal bronchopulmonary C-fibres (Taylor-Clark & Undem 2010).

For relationships for ozone-induced airway injury and the induction of acute inflammation, the literature is thinner, largely related to the greater technical challenges involved in obtaining this information for human subjects. An attempt to examine these relationships was published at the tail end of 2004 (Mudway & Kelly, 2004), which appeared to show near linear relationships between ozone-induced neutrophilia and inhaled dose and indicated a threshold by considering regression through the normal population range for airway neutrophils. These data tended to suggest that the threshold of ozone-induced inflammation was somewhat higher than that for lung function changes. With respect to this question, Kim et al. (2011) exposed 59 healthy, exercising young adults to 0.06 ppm ozone for 6.6 hours under controlled chamber conditions and reported a significant and acute decrease in FEV1 and increased neutrophilic inflammation of the airways, sampled using induced sputum. Of note, this paper found no influence of possession of the GSTM1 null genotype on the responses observed. Alexis et al. (2010) also demonstrated changes in inflammatory cell phenotype at this low ozone concentration. The cardiovascular effects of ozone in experimental studies remain ambiguous (Kusha et al., 2012). Generally speaking, the findings related to ozone are not as marked as those associated with exposures to concentrated ambient particles or diesel-engine exhausts.

Importantly, and consistent with earlier studies, the evidence presented since 2005 does not support a simple concordance between ozone-induced inflammation, lung function changes, pulmonary injury and cardiovascular effects (Que et al., 2011; Tank et al., 2011). It is therefore necessary that any discussion that implies thresholds for acute response end-points from human chamber studies is not interpreted in an overly simplistic manner. The absence of a small lung function decrement at a low ozone concentration does not imply the absence of adverse responses in other end-points. For this reason, plus the difficulty in relating acute changes in small groups of healthy young adults to chronic effects in sensitive subgroups at the population level, we have not emphasized the results of the chamber studies, in the discussion of thresholds for short- and long-term health effects. That there is data that suggests adverse acute responses in healthy subjects at, or near, the current WHO and EU guideline concentrations clearly suggests that the current standards warrant careful review, as the threshold in vulnerable groups is likely to be below these concentrations.

Question B3

Based on currently available health evidence, what ozone metrics, health outcomes and concentration–response functions can be used for health impact assessment?

Answer

It is mainly adverse health outcomes with known baseline rates that are suited for health impact assessments, typically mortality and hospital admissions. Evidence from time-series studies of short-term exposure to ozone suggests health impact assessment calculations can be undertaken for a range of end-points, including all-age, all-cause, cardiovascular and respiratory mortality and, for the age group 65 years and older, respiratory and cardiovascular hospital admissions. The epidemiological evidence supports calculations that use all-year coefficients for daily maximum 8-hour ozone (scaled from the 1-hour measures reported in the literature), including adjustment for PM₁₀.

For the reasons stated in the Answer to Question B2, we recommend that health impact calculations for short-term exposures assume linear concentration–response relationships for the outcomes recommended. Since the epidemiological evidence on linearity does not extend down to zero, appropriate cut-off points for health impact assessments are therefore recommended: one at 20 µg/m³ (10 ppb) for daily maximum 8-hour ozone and one at 70 µg/m³ (35 ppb), for consistency with previous work using SOMO35 data.

Because of the uncertainties about the effects of long-term exposure to ozone reported in the Answer to Question B1, we suggest that health impact assessments for respiratory and cardiopulmonary mortality are undertaken as a sensitivity scenario. We recommend using coefficients from single-pollutant models taken from the American Cancer Society cohort study, assuming an association exists within the range of ozone concentrations studied.

Rationale

Epidemiological studies of long-term exposure

In several studies of long-term exposure, mean concentrations for summer months or the mean of daily peak hourly ozone are used as exposure variables.

There are few studies of the long-term effect of ozone on mortality, so results from the American Cancer Society cohort study on respiratory and cardiopulmonary mortality are the most appropriate to use for health impact assessment(s). Because of instability in the ozone concentration–response function in the two-pollutant models in the American Cancer Society cohort study, we recommend, as a sensitivity analysis for health impact assessments, the use of the single-pollutant model results for respiratory and cardiopulmonary mortality from Krewski et al. (2009) and Smith KR et al. (2009), respectively.

Epidemiological studies of short-term exposure

Concentration–response functions for ozone measured as 1-hour averages are available for all-age, all-cause, cardiovascular and respiratory mortality. Results are expressed as the percentage change in mortality associated with a 10-µg/m³ increase in maximum 1-hour average daily ozone concentrations. Using data provided in Gryparis et al. (2004), these can be rescaled for daily maximum 8-hour average ozone concentrations. To account for potential

confounding by particles in ambient air, it is recommended that results adjusted for PM₁₀ are used for health impact assessment. Results for other outcomes and/or age groups are available (Table 4).

Concentration–response functions for ozone measured as 1-hour averages are available for age-specific (older than 65 years) cardiovascular and respiratory hospital admissions. These can be converted to 8-hour average ozone concentrations, as indicated above. The systematic review by Ji, Cohan & Bell (2011) provides evidence for age-specific respiratory subgroups for quantification in susceptible subgroups (Table 4) for daily maximum 8-hour ozone concentration.

Experimental studies

It is possible, and considerable effort has been invested since the 2005 global update of the WHO air quality guidelines, to derive exposure–response functions for ozone-induced transient decrements in lung function (McDonnell et al., 2012; Schelegle et al., 2012). While the studies by McDonnell et al. (2012) and Schelegle et al. (2012) support the presence of response thresholds in the healthy adult population, they also highlight the considerable heterogeneity of individual responses around the mean response at any given dose. Also, while these responses may be informative in interpreting short-term effects, it still remains uncertain how the responses reported in healthy subjects relate to those likely to occur in more vulnerable populations. These data are not easily related to long-term health effects.

Question B4

Is there evidence that other photochemical oxidants (individually or in mixtures) are of public health concern – for example, does the impact of outdoor ozone on reaction products indoors explain the outdoor ozone associations, and links to the secondary organic aerosol?

Answer

To date, the number of studies that address the toxicity of the products of the reaction of ozone with volatile organic compounds, particles and indoor surfaces is limited. It is clear, however, that ozone is involved in the formation of secondary inorganic and organic PM in the outdoor environment and that the reaction of ozone with common indoor volatile organic compounds generates a plethora of compounds, many of which have been proposed to be respiratory irritants. The field is currently positioning itself to perform whole animal and human exposure studies, to address whether the formation of these species, at relevant concentrations, constitutes a public health concern over and above that of ozone alone. At this time, however, there is insufficient information to make a definitive statement about Question B4.

Rationale

The photochemical processes that occur in ambient air, resulting in the formation of tropospheric ozone, also generate a range of other compounds, including formaldehyde, hydroperoxides, peroxides, peroxyacetyl nitrate, nitric acid and sulfuric acid. The available data on the toxicity of these compounds is limited and has not evolved significantly since 2005. Inhalation challenges (2 hours) of Sprague-Dawley rats with high concentrations of hydrogen peroxide vapour (10, 20 and 100 ppb) in the presence or absence of ammonium sulfate fine PM were found to elicit only minimal evidence of airway inflammation immediately and 24 hours after exposure (Morio et al., 2001). Similarly, experimental studies in mice and rats using high concentrations of peroxyacetyl nitrate have demonstrated pulmonary injury and increased susceptibility to infection, but only at concentrations well outside the ambient range (reviewed in Vyskocil, Viau & Lamy, 1998). At this time, therefore, there is no strong scientific justification for considering these photochemical oxidants as a public health concern.

Epidemiological studies rely largely on exposures attributed to ozone, based on outdoor concentrations measured at background locations. It is well established, however, that the populations studied spend only a small fraction of their daily lives in the outdoor environment and, as such, that there is a significant risk of exposure misclassification. Numerous studies have reported poor correlations between indoor and outdoor ozone concentrations, as well as between outdoor and personal exposures (Geyh et al., 2000). Clearly, the strength of the correlation between personal and fixed-site ozone measurements reflects the individual's time activity patterns, as well as the housing characteristics that govern the levels of air exchange, such as open windows and the prevalence of air-conditioning (Brauer & Brook, 1995; Liu et al., 1995, 1997; Romieu et al., 1998).

Unsurprisingly, given the reactive nature of ozone, indoor concentrations are typically lower in the absence of a defined indoor source. This reflects the rapid removal of ozone penetrating into the indoor environment, through its reaction with gaseous species and

particulates within indoor air (reviewed in Weschler, 2011), as well as reactive surfaces (Nicolas, Ramalho & Maupetit, 2007). These reactions occur with airborne- and surface-associated compounds as diverse as terpenoids, such as limonene (Weschler, 2011), human skin lipids (Wisthaler & Weschler, 2010), environmental tobacco smoke (Sleiman et al., 2010) and third-hand smoke (Petrick, Svidovsky & Dubowski, 2011), resulting in the formation of new gaseous or particulate species, many of which are established respiratory irritants. Taking limonene as an example, its oxidation by ozone can generate formaldehyde and acrolein, formic and acetic acids, alcohols, terpene derivatives (Clausen et al., 2001; Chen, Hopke & Carter, 2011), carbonyl compounds (Forester & Wells, 2009), radicals of varying stability (Chen & Hopke, 2010), and secondary organic aerosols, in the fine to ultrafine size range (Weschler, 2006; Wolkoff et al., 2008).

As many of these compounds have known irritant properties in the airways, it has been proposed that their formation might account for some of the health effects reported in the epidemiological literature (Weschler, 2011). For example formaldehyde is a documented sensory irritant that has been implicated in a worsening of allergic and respiratory symptoms in children (McGwin, Lienert & Kennedy, 2010). This argument is not limited to the consideration of indoor air; it applies also to ambient air, where ozone could be viewed as a chemical surrogate for all of its subsequent ozonation products.

This view has gained credence since 2005, largely as a result of attempts to explain the intercity variation in short-term ozone mortality coefficients reported in NMMAPS. Initially, Bell & Dominici (2008) examined whether this heterogeneity could be explained by differences in community-specific characteristics, identifying a higher prevalence of central air conditioning as one of several factors associated with reduced ozone-related mortality. A subsequent study by Chen, Zhao & Weschler (2012) found that a considerable degree of this variation could be accounted for by consideration of building ventilation, as a proxy for indoor ozone penetration, and one may speculate about its associated indoor chemistry. Consistent with the view that ozone penetrating into the indoor environment can drive the formation of irritant species, associations have been observed between ambient concentrations and upper airway, eye and neurological subjective symptoms in office workers, parallel to increased indoor aldehyde concentrations, consistent with ongoing ozone chemistry (Apte, Buchanan & Mendell, 2008). There is also evidence that ozone penetrating indoors can potentiate the irritant potential of household dust. Subjects exposed in climate-controlled chambers to resuspended office dust with ozone (300 ppb) for 3 hours displayed reduced peak expiratory flow and an increase in subjective symptoms compared with dust or ozone only exposures (Møhlhave et al., 2005). Similar results have been observed following limonene oxidation at more environmentally pertinent ozone levels (Tamás et al., 2006).

To date, the experimental evidence that addresses the toxicity of ozone oxidation products is limited, with rather simplistic *in vitro* experiments having been performed (McWhinney et al., 2011; Jang, Ghio & Cao, 2006). For example, McWhinney et al. (2011) demonstrated increased redox activity of particles generated from a two-stroke gasoline engine following ozonation, primarily related to the deposition of a redox-active secondary organic aerosol. This finding was interpreted as supporting the contention that the redox properties of ambient PM are enhanced with ageing in the presence of ozone. The earlier study by Jang, Ghio & Cao (2006) demonstrated that an absorbed secondary organic aerosol, formed between the reaction of ozone and α -pinene, increased the inflammatory properties of magnetic nanoparticles on a bronchial epithelial cell line. These and other recent papers do, however, demonstrate that the field is positioning itself to perform both whole animal and human

exposures in experimental smog chambers (Papapostolou et al., 2011). Some studies have examined impacts of ozone and the aged aerosol on heart function (ST-segment depression); but while these have found associations with primary combustion aerosols, there appeared to be no effect with ozone or the ozone-aged particles (Delfino et al., 2011). A study in rats exposed to limonene ozone reaction products did demonstrate induction of inflammation and stress responses, associated with pulmonary pathology, but the exposure was not easily related to the real-world situation (Sunil et al., 2007). Evidence that oxidation of the primary organic aerosol alters (and might potentiate) its toxicity was recently reported by Rager et al. (2011), who exposed an immortalized lung epithelial cell line to real world aerosols, either during the morning or the afternoon, the latter reflecting a more oxidized aerosol. The responses of the cells to these differing aerosols were profiled by transcriptomics, revealing a more robust transcriptional response as the primary aerosol aged.

With regard to the question asked, the current evidence on ozone oxidation products within the indoor, but also within the outdoor, environment suggests that they may affect human health. The data available at this time is, however, rather scant and insufficient to support any recommendation, beyond the need for further research in this area.

C. Proximity to roads, NO₂, other air pollutants and their mixtures

Question C1

There is evidence of increased health effects linked to proximity to roads. What evidence is available that specific air pollutants or mixtures are responsible for such increases, taking into account co-exposures such as noise?

Answer

Motor vehicles are a significant source of urban air pollution. Adverse effects on health due to proximity to roads were observed after adjusting for socioeconomic status and after adjusting for noise. Elevated health risks associated with living in close proximity to roads is unlikely to be explained by PM_{2.5} mass since this is only slightly elevated near roads. In contrast, levels of such pollutants as ultrafine particles, carbon monoxide, NO₂, black carbon, polycyclic aromatic hydrocarbons, and some metals are more elevated near roads. Individually or in combination, these are likely to be responsible for the observed adverse effects on health. Current available evidence does not allow discernment of the pollutants or pollutant combinations that are related to different health outcomes, although association with tailpipe primary PM is identified increasingly.

Exhaust emissions are an important source of traffic-related pollution, and several epidemiological and toxicological studies have linked such emissions to adverse effects on health. Road abrasion, tyre wear and brake wear are non-exhaust traffic emissions that become relatively more important with progressive reductions in exhaust emissions. Toxicological research increasingly indicates that such non-exhaust pollutants could be responsible for some of the observed adverse effects on health.

Rationale

In 2010, the Health Effects Institute published their authoritative report *Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects*, which formed the basis of the current assessment. Motor vehicles emit large quantities of carbon dioxide, carbon monoxide, hydrocarbons, nitrogen oxides, PM, and substances known as mobile source air toxics, such as benzene, formaldehyde, acetaldehyde, 1,3-butadiene and lead (where leaded gasoline is still in use). Furthermore, secondary by-products, such as ozone and secondary aerosols (for example, nitrates and inorganic and organic acids), are formed farther away from roads, but these are not considered here.

Pollutant emissions from vehicles are related to vehicle type (such as light- or heavy-duty vehicles) and age, operating and maintenance conditions, exhaust treatment, type and quality of fuel, wear of parts (such as tyres and brakes), and engine lubricants used. Important non-combustion PM emissions associated with motor vehicles include wear particles from road surfaces, tyres and brakes, as well as resuspended road dust.

Non-combustion emissions contain such chemical compounds as trace metals and organics. Traffic emissions are the principal source of intra-urban variation in the concentrations of air pollutants in many cities, but this can vary both by time and location.

The Health Effects Institute report summarized that measurements of outdoor air quality on roadways indicate that concentrations of ultrafine particles, black carbon, particle-bound polycyclic aromatic hydrocarbons, nitric oxide, NO₂, carbon monoxide, benzene, and formaldehyde are high and variable compared with ambient concentrations measured at background locations. Furthermore, concentrations around roadways may represent direct influences from road traffic and from background concentrations. The concentration gradient also seems to be a function of the reactivity of specific pollutants, such as NO₂, nitrogen oxides and ozone. Hitchins et al. (2000) reported a 50% decrease in PM_{2.5} and ultrafine particles within 100–150 m of a road. A decay to background concentrations within as little as 50 m has been described for PM_{2.5} mass concentration (Tiitta et al., 2002), although PM_{2.5} tends to be more spatially homogeneous than ultrafine particles. Roorda-Knape et al. (1998) found that concentrations of black smoke, PM_{2.5}, NO₂, and benzene decreased to background concentrations within 100–150 m of a roadway (Roorda-Knape et al., 1998).

In an environment with greater volumes of traffic, Zhu et al. (2002) found that ultrafine particles, black carbon, and total PM counts decreased rapidly in the first 150 m and then levelled off. PM_{2.5} was found to be elevated only modestly (that is, in the range of 20%) near roadways. Zhu et al. (2006) suggested that distance-decay gradients extend to at least 500 m on the downwind side during night-time hours. Some studies concurrently measured such pollutants as NO₂ and volatile organic compounds (Roorda-Knape et al., 1998; Weisel et al., 2005) and carbon monoxide (Zhu et al., 2002; Zhang et al., 2005), to assess pollutant mix. Zhu et al. (2002) found that the decay of concentrations with distance on the downwind side of a highway was similar for ultrafine particles, black carbon and carbon monoxide – that is, a 60% to 80% decrease from roadside concentrations within 100 m. Gilbert et al. (2003) also found that NO₂ concentrations decayed with distance around a busy highway in Montreal, the greatest decrease occurring within the first 200 m.

In general, distance-decay gradients have different characteristics on upwind and downwind sides of an expressway (Roorda-Knape et al., 1998; Zhu et al., 2002; Gilbert et al., 2003; McConnell et al., 2006b). On the upwind side, concentrations drop off to near background levels within 200 m and, in the case of particles, probably within 100 m or less. On the downwind side, concentrations do not generally reach background levels until 300–500 m. In some studies, this was extended to up to 1500 m for NO₂ (Gilbert et al., 2003; Jerrett et al., 2007) and 800 m for ultrafine particle number counts (Reponen et al., 2003).

Zhou & Levy (2007) pooled estimates from more than 30 studies and characterized the decay with distance from the road source for various combinations of reactive and nonreactive pollutants in areas of either high or low background pollution. Further simulations, using dispersion models, were employed to augment the empirical results. Overall, the distance-decay gradients demonstrated a heterogeneity that could be explained by background concentrations, pollutant characteristics, and local meteorological conditions (such as wind speed). Based on dispersion simulations for elemental carbon, the distance-decay gradient was in the range of 100–400 m from the source. For ultrafine particle counts, the gradient was 100–300 m; NO₂ had gradients of 200–500 m. Also, metals (Peachey et al., 2009) and polycyclic aromatic hydrocarbons (Schnelle-Kreis et al., 1999) have shown a distance-decay gradient for roads. While this chapter was being prepared, Karner, Eisinger & Niemeier (2010) published a systematic compilation of the proximity measurements of multiple pollutants classified by category, which is a useful addition to this discussion.

In conclusion, there are a number of studies showing higher levels of pollutants in proximity to roads. In general PM_{2.5} does not exhibit the sharp distance-decay gradient evident for carbon monoxide, NO₂ or ultrafine particles. The Health Effects Institute Panel identified an exposure zone within a range of up to 300–500 m from a highway or a major road as the area most highly affected by traffic emissions – the range reflecting the variable influence of background pollution concentrations, meteorological conditions, and season. Metals usually attributed to brake and tyre wear, with such metals as copper, iron, antimony, tin, barium and zinc being higher close to roadways, compared with urban background (Querol et al., 2007). These metals were previously only seen in industrialized areas (Lee, Garland & Fox, 1994). Importantly, Ostro et al. (2011) found association between PM_{2.5} road dust and mortality.

Many studies have shown excess health risks in proximity to roads – after adjustment for a range of possible confounders, including socioeconomic status – for such outcomes as: cardiovascular mortality (Gehring et al., 2006), respiratory mortality and traffic intensity in a 100-m buffer (Beelen et al., 2008a), myocardial infarction (Tonne et al., 2007), cardiovascular disease (Hoffmann et al., 2006), coronary artery calcification (Hoffmann et al., 2007), cardiac function-left ventricular mass index (van Hee et al., 2009), asthma (Morgenstern et al., 2007, 2008; Gauderman et al., 2005; McConnell et al., 2006a; Gordian, Haneuse & Wakefield, 2006; Kim et al., 2008), wheeze (McConnell et al., 2006a; Ryan et al., 2005; Venn et al., 2005; Gauderman et al., 2005; van Vliet et al., 1997), asthma hospitalization (Edwards, Walters & Griffiths, 1994; English et al., 1999; Lin et al., 2002; Wilhelm et al., 2008), lung function reduction (Sekine et al., 2004; Kan et al., 2007; Gauderman et al., 2007; Schikowski et al., 2007), birth weight (Brauer et al., 2008), childhood cancer (Savitz & Feingold, 1989; Pearson, Wachtel & Ebi, 2000), and lung cancer (Beelen et al., 2008b). Therefore, the observed excess risk in proximity to roads cannot solely be explained by socioeconomic status; although associations between traffic proximity and health impacts have been observed in locations where both high and low socioeconomic status occur in close proximity to roads (Généreux et al., 2008), its influence cannot be ruled out.

Some studies have examined the effects of air pollution and noise at the same time. Those who have done so found that excess risks of air pollution in the proximity of roads generally remained after adjustment for noise for cardiovascular mortality (Beelen et al., 2008a; Gan et al., 2012), hypertension and diabetes mellitus (Coogan et al., 2012), hypertension (Fuks et al., 2011; Sørensen et al., 2012), and cognitive performance of primary schoolchildren (van Kempen et al., 2012). Therefore, these studies show effects of air pollution that cannot be explained by noise.

Generally, few epidemiological studies have examined the health effects of multiple air pollutants in proximity to roads. For those studies that have examined multiple air pollutants, it is not clear whether or not these pollutants are coming solely from roads and/or traffic or not. Some studies have examined the effect of multiple pollutants in the proximity of roads, but their small number, the generally high correlation among different pollutants, and the inconsistent results do not provide a good basis to draw firm conclusions.

The only epidemiological study identified that evaluates the short-term effects of multiple air pollutants in proximity to roads and farther away is by Roemer & van Wijnen (2001). These investigators obtained data from a sample of Amsterdam residents ($n = 4352$) who lived “along roads with more than 10,000 motorized vehicles per day” (actual distance from the roads not specified) from 1987 to 1998, and these were compared with the general

population. Ambient-pollutant data from “traffic-influenced” sites and “non-influenced” sites (criteria not specified) were obtained for black smoke, PM₁₀, and gaseous pollutants (carbon monoxide, NO₂, SO₂ and ozone). They found higher levels of NO₂, nitric oxide, carbon monoxide and black smoke at the traffic-influenced measurement sites compared with the background sites, confirming combustion engines as the source of these air pollutants. Black smoke and NO₂ were associated with mortality (RR: 1.38 and 1.10, respectively, for an increase of 100 µg/m³ on the previous day). Effect estimates were larger in the summer and in the population living along busy roads. Only 10% of the total Amsterdam population resides along busy roads. Nevertheless, they were still able to show associations between black smoke, NO₂, and daily mortality for this subpopulation. These associations were stronger than they were in the total population.

Other studies have examined the effects of multiple pollutants in the proximity of roads for respiratory health and allergic disease outcomes (Brunekreef et al., 1997; van Vliet et al., 1997; Nicolai et al., 2003; Kim J et al., 2004; Gauderman et al., 2005; Morgenstern et al., 2008; Rosenlund et al., 2009a; McConnell et al., 2010; Gehring et al., 2010; Clark et al., 2010; Gruzieva et al., 2012, 2013; Schultz et al., 2012; Willers et al., 2013), birth weight (Brauer et al., 2008), pre-eclampsia and preterm birth (Wu et al., 2011), fatal myocardial infarction (Rosenlund et al., 2006, 2009b), lung cancer (Nyberg et al., 2000) and mortality (Beelen et al., 2008a). However in their analyses these investigators used either a *proximity to road* measure or a specific pollutant(s), but never the effects of (multiple) pollutants within proximity to roads. Even so, and assuming that often the population may have been near roads, no consistent picture emerged that specific pollutants and/or a mixture may be responsible for the observed health effects.

COMEAP recently concluded that the epidemiological evidence for associations between ambient levels of air pollutants and asthma prevalence at a whole community level was unconvincing; a meta-analysis confirmed a lack of association (Gowers et al., 2012). In contrast, a meta-analysis of cohort studies found an association between asthma incidence and within-community variations in air pollution (largely traffic dominated). Similarly, a systematic review suggested an association between asthma prevalence and exposure to traffic, although only in those living very close to heavily trafficked roads carrying many trucks, suggesting a possible role for diesel exhaust.

A critical review of the literature on the health effects of traffic-related air pollution (HEI, 2010b) included toxicological evidence of the impact of traffic-mixture exposures. Such evidence stems from controlled exposures of animals in areas of high traffic density, real-world exposure design in which subjects spend time in a polluted location (compared with equivalent activities in a location with relatively clean air), and individuals occupationally exposed to traffic and populations (animals or human beings) naturally exposed to polluted urban environments.² Of the small number of studies reported (compared with the much larger literature on specific components of traffic emissions), the main cardiorespiratory findings in humans were that short-term exposures can bring about decrements in lung function and enhanced responses to allergens in adult subjects with asthma (Svartengren et al., 2000; McCreanor et al., 2007), as well as positive and negative effects on vascular function in healthy subjects (Rundell et al., 2007; Bräuner et al., 2008). On-road animal

² Note. It is not possible, in such experimental settings, to separate traffic-related pollutants from those derived from other sources, and this may be the case, in particular, in the field studies of Mexico City, where ozone is the most important pollutant in terms of frequency of occurrence of high levels, persistence and spatial distribution.

studies, utilizing compromised or allergic rodents, observed mild pulmonary inflammation (Elder et al., 2004), significant alterations in lung structure and elastic properties (Mauad et al., 2008), and systemic inflammation and effects on vascular function and autonomic control of the heart (Elder et al., 2004, 2007). Effects on reproductive and neurological health – specifically, compromised sperm quality in toll booth employees (de Rosa et al., 2003) and neuropathological lesions in dogs exposed to high concentrations of ambient pollution in Mexico City (Calderón-Garcidueñas et al., 2002) – were interpreted with caution as a result of data limitations. Finally, observations of genotoxic effects were limited to one study that reported higher mutagenicity from total suspended particulates in an area with intense moving traffic than in an area with limited traffic (Bronzetti et al., 1997).

In a recent review of the adverse effects on health of black carbon, the WHO Regional Office for Europe (2012) evaluated the toxicological evidence of effects of diesel exhaust in controlled human exposure experiments. It concluded that there are not enough clinical or toxicological studies to allow an evaluation: of the qualitative differences between the health effects of exposure to black carbon or those of exposure to PM mass (for example, different health outcomes); of a quantitative comparison of the strength of the associations; or of (identifying) any distinctive mechanism of black carbon effects. The review of the results of all available toxicological studies suggested that black carbon (measured as elemental carbon) may not be a major directly toxic component of fine PM, but it may operate as a universal carrier of a wide variety of combustion-derived chemical constituents of varying toxicity to sensitive targets in the human body, such as the lungs, the body's major defence cells and, possibly, the systemic blood circulation.

Recent noteworthy toxicological evidence on the effects of traffic-mixture exposures include increased respiratory symptoms, decreased peak expiratory flow and an inflammatory response in the upper airways in mild asthmatic adults exposed for 2 hours in a road tunnel (Larsson et al., 2010). Studies of acute (20 minutes to 2 hours) effects of real-life traffic exposure on healthy volunteers have been unremarkable and are limited to a small increase in the percentage of blood neutrophils (Jacobs et al., 2010), modest effects on peak flow, exhaled nitric oxide and airway resistance (Zuurbier et al., 2011a, b). A study by Strak et al. (2012) was specifically designed to evaluate the contribution of different pollutants. They increased exposure contrasts and reduced correlations among pollutants by exposing healthy volunteers at five different locations, including two traffic sites. Changes in particle number concentrations, NO₂, and nitrogen oxides during five-hour exposures were associated with increased exhaled nitric oxide and impaired lung function. These associations were robust and insensitive to adjustment for other pollutants. PM mass concentration or other PM characteristics, including elemental carbon and trace metals, were not predictive of the observed responses. Results for several other health end-points, including markers of cardiovascular effects, have not yet been published.

Two toxicological studies have investigated acute cardiovascular health effects in volunteers with type 2 diabetes. Passengers on 90–110 minute car rides on a busy road demonstrated a decrease in high-frequency heart rate variability and an increase in the ratio of low-frequency to high-frequency components compared with pre-ride measurements (Laumbach et al., 2010). Chronic exposure to urban air pollution (in chambers 20 m from a street with heavy traffic in downtown Sao Paulo) exacerbates the susceptibility of low density lipoprotein to oxidation, atherogenesis and vascular remodelling in hyperlipidemic mice (Soares et al., 2009), and in Swiss mice it presents as coronary arteriolar fibrosis and elastosis (Akinaga et al., 2009).

Toxicological reproductive outcomes have been investigated in subjects occupationally exposed to traffic. Findings include abnormal sperm count, mobility and morphology (Güven et al., 2008) and a significantly higher percentage of spermatozoa with damaged chromatin and DNA fragmentation (Calogero et al., 2011) in toll-gate workers. In male traffic policemen, lower free testosterone (Sancini et al., 2011) and higher luteinizing hormone (Tomao et al., 2009) and follicle-stimulating hormone (Tomei et al., 2009) plasma levels were reported. Studies on female traffic police observed significantly higher plasma free testosterone (Tomei et al., 2008) and follicle-stimulating hormone levels during the proliferative phase of the menstrual cycle (Ciarrocca et al., 2011).

Evidence continues to accumulate on the role that oxidative stress has as a mechanism through which traffic-related air pollution causes adverse effects on human health. The validity of urinary excretion of 8-oxo-7,8-dihydro-2-deoxyguanosine (8oxodG) as a biomarker was recently demonstrated in a meta-analysis (Barbato et al., 2010). Oxidative damage to DNA and the formation of bulky adducts are two mechanisms by which traffic-related air pollution could lead to mutagenesis and, ultimately, cause cancer. Bulky DNA adducts have been detected among traffic-exposed workers (Palli et al., 2008) and – together with micronuclei – in cord blood after maternal exposures to traffic-related air pollution, suggesting that transplacental environmental exposures could induce DNA damage in neonates (Pedersen et al., 2009).

Ambient PM – particularly that derived from vehicles – has high oxidative potential (Kelly, 2003), and a clear increment in roadside particulate oxidative potential has been found that appears to be associated with metals arising from engine abrasion (iron, manganese and molybdenum) or brake wear (copper and antimony) (Schauer et al., 2006; Thorpe & Harrison, 2008). The roadside increments of particulate oxidative potential are significant and the metal components identified as determinants of this oxidative activity have established toxicity in human beings (Kelly et al., 2011). These results are potentially important as they highlight the contribution of traffic non-exhaust pollutants that are not regulated currently.

Question C2

Is there any new evidence on the health effects of NO₂ that impact upon the current limit values? Are long-term or short-term limit values justified on the grounds that NO₂ affects human health directly, or is it linked to other co-emitted pollutants for which NO₂ is an indicator substance?

Answer

Many studies, not previously considered, or published since 2004, have documented associations between day-to-day variations in NO₂ concentration and variations in mortality, hospital admissions, and respiratory symptoms. Also, more studies have now been published, showing associations between long-term exposure to NO₂ and mortality and morbidity. Both short- and long-term studies have found these associations with adverse effects at concentrations that were at or below the current EU limit values, which for NO₂ are equivalent to the values from the 2005 global update of the WHO air quality guidelines. Chamber and toxicological evidence provides some mechanistic support for a causal interpretation of the respiratory effects. Hence, the results of these new studies provide support for updating the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) for NO₂, to give: (a) an epidemiologically based short-term guideline value; and (b) an annual average guideline value based on the newly accumulated evidence. In both instances, this could result in lower guideline values.

There is evidence of small effects on inflammation and increased airway hyperresponsiveness with NO₂ per se in the range of 380–1880 µg/m³ (0.2–1.0 ppm). The evidence for these effects comes from chamber studies (under a broad range of exposure conditions, with exposure durations of 15 minutes to 6 hours, with some inconsistency in results), with more marked, consistent, responses observed from 1880 µg/m³ (1.0 ppm). New review reports suggest weak to moderate lung cell changes in animal studies at one-hour concentrations of 380–1500 µg/m³ (0.2–0.8 ppm). These concentration ranges are not far from concentrations that occur at roadsides or in traffic for multiple hours. The chamber studies examined small numbers of healthy or mildly asthmatic subjects, whereas the general population will include subjects who are more sensitive and may therefore experience more pronounced effects at lower concentrations.

The associations between NO₂ and short-term health effects in many studies remain after adjustment for other pollutants. The pollutants used in the adjustments include PM₁₀, PM_{2.5}, and occasionally black smoke. This does not prove that these associations are completely attributable to NO₂ per se, as NO₂ in these studies may also represent other constituents (which have adverse effects on health) not represented by currently regulated PM metrics. As there is consistent short-term epidemiological evidence and some mechanistic support for causality, particularly for respiratory outcomes, it is reasonable to infer that NO₂ has some direct effects.

It is much harder to judge the independent effects of NO₂ in the long-term studies because, in those investigations, the correlations between concentrations of NO₂ and other pollutants are often high, so that NO₂ might represent the mixture of traffic-related air pollutants. In this case, chamber studies do not apply and toxicological evidence is limited. However, some epidemiological studies do suggest associations of long-term NO₂ exposures with respiratory and cardiovascular mortality and with children's respiratory symptoms and lung function that

were independent of PM mass metrics. As with the short-term effects, NO₂ in these studies may represent other constituents. Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations are suggestive of a causal relationship.

Rationale

This question is particularly important at this time as, in Europe, decreasing annual trends in carbonaceous aerosols have generally been observed, probably reflecting the impact of the Euro 4 and 5 vehicle standards in reducing diesel PM emissions; however, NO₂ has not been declining in the same way or has even been increasing. This may result in very different ratios of NO₂ to organic and elemental carbon emissions (supplemental material available illustrating this difference is upon request) and changes in ratios of concentrations (see discussion). This change in ratio has implications for the interpretation of NO₂ as a quantitative proxy for PM vehicle pollution and illustrates the need to understand the effects of NO₂ per se.

The text below sets out the short-term epidemiological, chamber study and toxicological evidence and then the long-term epidemiological and toxicological evidence before integrating the evidence and discussing the implications for the guidelines. Although the uncertainty over the long-term guideline has greatest policy importance, the short-term evidence is considered first because it provides support for the plausibility of the long-term effects. It should be emphasized that it was not our remit to review all studies, just those published since 2004, using reviews by others where necessary. Not all areas – for example, birth outcomes – have been reviewed in detail, due to time constraints or lack of implications for the conclusions. Also, our remit was not to actually propose new air quality guidelines, just to advise whether the guidelines needed to be revised in the light of scientific evidence published since the last revision of the guidelines (WHO Regional Office for Europe, 2006). Further detailed consideration will be needed at the guideline setting stage.

1. Short-term guideline

1.1 Time series evidence

The time-series evidence on NO₂ has increased since the 2005 global update of the WHO air quality guidelines. Since 2004 (the cut-off date for studies included in the last WHO review), 125 new peer-reviewed ecological time-series studies on NO₂ have been published up to April 2011. These were identified using the Air Pollution Epidemiology Database (APED).³ Table 5 shows the total number of studies, according to health outcomes examined and the number of multicity studies available.

The new studies were conducted mainly in the WHO Western Pacific Region (which includes China), Europe, the United States and Canada. The majority used 24-hour average concentrations of NO₂, measured mainly at urban background locations. A few studies published after the April 2011 cut-off for APED were included in the review, as they contain information on issues of relevance to the Question. These are not reflected in Table 5, but are discussed in the text which follows. A list of all time-series references considered in this

³ APED contains peer-reviewed ecological time-series studies published up to April 2011 – that is, the cut-off date for the last update of its literature search. A description of APED can be found in Anderson et al. (2007).

project is available upon request. Only a selection of these references is discussed in the text below.

Given the crucial issue of understanding whether NO₂ has direct adverse effects on health, emphasis has been placed on time-series studies that investigated whether associations of NO₂ are robust to adjustment of concentrations of particles (and other pollutants). More than 65 time-series studies of NO₂ that used two-pollutant and/or multipollutant statistical models are available – only a proportion of these included adjustment for a metric of PM, and these are discussed in the sections that follow.

Table 5. Summary of ecological time-series studies of NO₂ in APED

WHO region(s)/ averaging time	Total	Multi-city study	Outcome			
			Hospital admission	Mortality	Emergency room visit	Other ^a
All	125	23	59	52	19 ^b	2
WHO region						
AMR A	25	7	9	7	9	0
AMR B	5	0	2	1	4	1
EMR B	1	0	1	0	0	0
EUR A	41	10	18	21	4	0
SEAR B	1	1	0	1	0	0
SEAR D	1	0	1	0	0	0
WPR A	12	5	7	4	1	0
WPR B	40	1	21	19	1	1
Multi-regional ^c	1	1	0	1	0	0
Averaging time						
1-hour	19	6	11	4	5	0
24 hours	107	16	50	47	14	2
NA	1	1	0	1	0	0

NA: not available – the averaging time of one paper (multi-city on mortality) was unknown.

WHO regions: AMR: Americas; EMR: Eastern Mediterranean; EUR: Europe; SEAR: South-East Asia; WPR: Western Pacific; A: very low child and adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality.

^a Other includes consultations with general practitioners and outpatient visits – for studies published from 2004 to May 2009.

^b Emergency room visits – for studies published from 2004 to May 2009.

^c A multi-city study (on mortality) considered two WHO regions (SEAR B and WPR B) – this is also reflected in the individual totals for these WHO region categories in the table.

Note. Two papers (on hospital admissions) used more than one averaging time – that is, 1 hour and 24 hours. Seven papers examined more than one health outcome.

Mortality

In the 2005 global update of the WHO air quality guidelines, WHO concluded that daily concentrations of NO₂ are associated significantly with increased daily all-cause, cardiovascular and respiratory mortality within the range of concentrations studied; however, it also noted the reductions in the overall effect estimates in an important meta-analysis, following adjustment for PM (Stieb, Judek & Burnett, 2002, 2003). Since then, comprehensive reviews of the time-series literature on NO₂ have emerged with similar conclusions – that is, the short-term associations of NO₂ with mortality are suggestive of a direct effect, but there is some uncertainty about the causal nature of these associations (CARB, 2007; EPA, 2008b). In addition to these, a peer-reviewed research report of a comprehensive systematic review and meta-analysis of single pollutant model estimates

(Anderson et al., 2007) reported that increases in NO₂ concentrations (per 10 µg/m³, 24-hour averages) are associated with increases in all-cause mortality: 0.49% (95% CI: 0.38–0.60%) in all ages and 0.86% (95% CI: 0.50–1.22%) for those older than 65 years of age. Results for maximum 1-hour average concentrations of NO₂ were lower: 0.09% (95% CI: -0.01–0.20%) and 0.15% (95% CI: 0.03–0.26%) in all-ages and for those older than 65 years of age, respectively. Increases in daily mortality, for all ages, for cardiorespiratory mortality (0.18% (95% CI: 0.08–0.27%), 24-hour average); cardiovascular mortality (0.34% (95% CI: 0.19–0.48%), maximum 1-hour average, 1.17% (95% CI: 0.82–1.53%), 24-hour average); and respiratory mortality (0.45% (95% CI: 0.21–0.69%), maximum 1-hour average, 1.76% (95% CI: 1.35–2.17%), 24-hour average) were also reported with NO₂. Anderson et al. (2007) also compared multipollutant model estimates for NO₂ from multicity studies and reported that consistent positive estimates for mortality (and hospital admissions) were found before and after adjustment for co-pollutants, with the size and precision of the estimates not being substantially reduced after such adjustment. The authors also concluded that these findings suggested that the short-term associations between NO₂ and health outcomes were unlikely to be confounded by other pollutant measures.

Twenty-four time-series studies of mortality, which used two-pollutant and/or multipollutant models for NO₂, have been published since the 2005 global update of the WHO air quality guidelines (Burnett et al., 2004; Dales et al., 2004; Kan, Jia & Chen, 2004a,b; Zeka & Schwartz, 2004; Simpson et al., 2005a; Díaz, Linares & Tobías, 2006; Samoli et al., 2006; Brook et al., 2007; Qian et al., 2007, 2010; Yamazaki et al., 2007; Chen et al., 2008; Hu et al., 2008; Ren Y et al., 2008c; Wong et al., 2008; Breitner et al., 2009; Chen et al., 2010a; López-Villarrubia et al., 2010; Park, Hong & Kim, 2011; Chiusolo et al., 2011; Chen et al., 2012a,b; Faustini et al., 2012; Chen et al., 2013).⁴ All of these papers included adjustments for a metric of PM; 17 of the 24 papers reported positive, though not always statistically significant, short-term associations of NO₂ with mortality for a range of diagnoses and age groups, after adjustment for a PM metric.

Multicity studies (of the aforementioned 24 studies), which included adjustment for particles in two-pollutant models, show robust short-term associations of NO₂ with increased all-cause, cardiovascular and respiratory mortality (Table 6), though some evidence of confounding (by black smoke) of the NO₂ association with respiratory mortality was identified in the European study, APHEA-2.⁵ Mainly PM₁₀ was used when controlling for particles in these multicity studies. In contrast, the large American multicity study, NMMAPS, did not find such associations between NO₂ and daily mortality: only a small and non-significant association of NO₂ with all-cause mortality was reported after adjustment in a two-pollutant model with PM₁₀; no association was found in a multipollutant model, which included PM₁₀, carbon monoxide, SO₂ and ozone (Zeka & Schwartz, 2004; see Table 6). Previous NMMAPS analyses of a subset of the 90 cities in the United States in this study found approximately a 0.7% (95% CI: 0.3–1.2%)⁶ increase in all-cause mortality per

⁴ Chiusolo et al. (2011), Chen et al. (2012a,b), Faustini et al. (2012) and Chen et al., 2013 were published after the last update of APED in April 2011 and are not presented in Table 5. Two further papers (Koop & Tole (2004) and Roberts & Martin(2005)), which explored approaches to estimating the health effects of multiple air pollutants, are also available and are included in the information presented in Table 5.

⁵ Faustini et al. (2012) compared deaths from all-causes and specific causes in the general population without chronic obstructive pulmonary disease with a chronic obstructive pulmonary disease cohort in Rome, Italy. Associations for all-cause and respiratory mortality were much stronger for NO₂ than for PM₁₀, with larger estimates in the chronic obstructive pulmonary disease cohort, especially for respiratory mortality.

⁶ Estimate taken from CARB (2007).

45.12 $\mu\text{g}/\text{m}^3$ (24 ppb)⁷ NO_2 at lag 1 (other lagged model results showed that the strongest association between NO_2 and all-cause mortality was identified at lag 1) (HEI, 2003). Following adjustment for PM_{10} or other pollutants (O_3 and SO_2), the central estimates either increased or were unchanged (based on a plot of the estimates), though they lost statistical significance (HEI, 2003). The reason for the difference between NMMAPS and the other multicity studies is unclear. We note that the method used by Zeka & Schwartz (2004) differed from those used in the other studies, as it sought to deal with measurement error. The shape of the concentration–response function in the multicity studies was often assumed to be linear. Samoli et al. (2006) reported that their assumption of a linear relationship between maximum 1-hour concentrations of NO_2 and mortality was based on other results from APHEA-2 (Samoli et al., 2003), which suggested that it was appropriate to make such an assumption. Where tested, the relationship between NO_2 and all-cause mortality did in fact appear to be linear (Wong et al., 2008; Chen et al., 2012b).

Some studies have examined changes in risk estimates following changes in the composition and levels of ambient pollutants in an attempt to identify possible causal agents within the ambient mixture (Fischer et al., 2011; Peters et al., 2009; Breitner et al., 2009) – these have been difficult to interpret, but a couple suggest that ultrafine particles may be important. Using data from 10 Canadian cities, Brook et al. (2007) examined whether NO_2 was acting as an indicator of other pollutants linked to vehicle emissions. The study concluded that NO_2 was a better indicator than $\text{PM}_{2.5}$ of a range of pollutants in motor vehicle exhaust, such as volatile organic compounds, aldehydes and particle-bound organics. In addition, NO_2 was regarded as a good indicator of polycyclic aromatic hydrocarbons. While the authors concluded that the strong effect of NO_2 in Canadian cities could be due to NO_2 acting as the best indicator (among the pollutants monitored) of motor vehicle combustion, they also noted that the findings do not rule out the possibility of NO_2 having a direct effect on mortality in the cities examined.

In summary, positive and statistically significant short-term associations of NO_2 with all-cause and cause-specific mortality have been reported in the new studies published since the 2005 global update of the WHO air quality guidelines. Robustness of the short-term NO_2 associations to adjustment for particles (mainly PM_{10} , and sometimes $\text{PM}_{2.5}$ or black smoke) and other pollutants has been demonstrated in multicity studies from various geographic locations, including Europe. The United States NMMAPS is, however, a notable exception. Overall, the findings suggest that the short-term associations of NO_2 with mortality are not confounded by the particle metrics used in the studies – that is, mainly PM_{10} , and sometimes $\text{PM}_{2.5}$ and black smoke. The limited number of studies that assessed confounding by ultrafine particles does not allow firm conclusions to be drawn for this issue.

⁷ 1ppb = 1.88 $\mu\text{g}/\text{m}^3$ – this has been used throughout the review of time-series studies.

Table 6. Summary of two-pollutant model results for NO₂ from multicity time-series and case-crossover studies of mortality

Reference, study location, age group	NO ₂ level	Correlation with PM	NO ₂ estimate (95% CI)	NO ₂ + PM estimate (95% CI)	PM estimate (95% CI)	PM + NO ₂ estimate (95% CI)	Comments
All-cause mortality							
Zeka & Schwartz (2004) 90 United States cities (NMMAPS) All ages	Not reported in the paper 24 hours	Not reported in the paper	Not reported in the paper	0.033% (CIs not reported) per 10 ppb (+PM ₁₀), lag 0-1	Not reported in the paper	0.16% (CIs not reported) per 10 µg/m ³ PM ₁₀ , lag 0-1	NO ₂ (+SO ₂ , O ₃ , CO) -0.004% (CIs not reported) PM ₁₀ (+SO ₂ , O ₃ , CO) 0.24% (0.05–0.42%)
Simpson et al. (2005a) 4 Australian cities All ages	Mean (1-hour max.): 30.7–44.5 µg/m ³ Range (1-hour max.): 3.5–125.4 µg/m ³	1-hour NO ₂ : 24-hour B _{sp} : 0.29–0.62	RR: 1.0012 (1.0004–1.0019) per 1.88 µg/m ³ NO ₂ , lag 0-1.	RR: 1.0010 (1.0001–1.0019) (+B _{sp})	RR: 1.0310 (1.0039–1.0589) per unit increase B _{sp}	RR: 1.0098 (0.9779–1.0427)	B _{sp} (an indicator of fine particles < 2 µm in diameter) –light-scattering by nephelometry
Samoli et al. (2006) 30 European cities (APHEA-2) All ages	Mean (1-hour max.): 46.2–154.8 µg/m ³	NO ₂ :BS: 0.11–0.78	Random effects estimate: 0.30% (0.22–0.38%) per 10 µg/m ³ NO ₂ , lag 0-1	Random and fixed effects: 0.33% (0.23–0.42%) per 10 µg/m ³ NO ₂ (+BS)	Katsouyanni et al. (2001) reported random effect estimates per 10 µg/m ³ :	Katsouyanni et al. (2001) reported adjusted random effect estimates per 10 µg/m ³ :	Fixed effect: 0.33% (0.23–0.42%) NO ₂ (+BS)
		NO ₂ :PM ₁₀ : 0.11–0.69		0.27% (0.16–0.38%) per 10 µg/m ³ NO ₂ (+PM ₁₀)	BS: 0.58% (0.3–0.8%) PM ₁₀ : 0.62% (0.4–0.8%)	BS: 0.26% (0.0–0.6%) PM ₁₀ : 0.41% (0.2–0.7%)	Fixed effect: 0.27% (0.20–0.34%) NO ₂ (+PM ₁₀)
Brook et al. (2007) 10 Canadian cities All ages	Only IQR reported: 19.34 µg/m ³ (24 hours)	NO ₂ :PM _{2.5} : 0.54 Range: 0.45–0.70	RR: 1.018 (1.007–1.028) per 19.34 µg/m ³ IQR NO ₂ , lag 1	RR: 1.016 (1.003–1.029) (+PM _{2.5})	RR: 1.009 (1.001–1.017) per 8.1 µg/m ³ IQR PM _{2.5}	RR: 1.002 (0.992–1.011) PM _{2.5}	--
		NO ₂ :PM _{10-2.5} : 0.31 Range: 0.04–0.50		RR: 1.017 (1.006–1.028) (+PM _{10-2.5})	RR: 1.007 (0.998, 1.0158) per 8.7 µg/m ³ PM _{10-2.5}	RR: 1.002 (0.993–1.012) PM _{10-2.5}	--
		NO ₂ :PM ₁₀ : 0.50 Range: 0.23–0.70		RR: 1.015 (1.003–1.028) (+PM ₁₀)	RR: 1.011 (1.002–1.020) per 14.9 µg/m ³ PM ₁₀	RR: 1.003 (0.992–1.014) PM ₁₀	--

Reference, study location, age group	NO ₂ level	Correlation with PM	NO ₂ estimate (95% CI)	NO ₂ + PM estimate (95% CI)	PM estimate (95% CI)	PM + NO ₂ estimate (95% CI)	Comments
Wong et al. (2008) 4 cities: 3 Chinese and 1 Thai city (PAPA) All ages	Mean (24 hours): 44.7–66.6 µg/m ³	NO ₂ :PM ₁₀ : 0.71–0.85	Excess risk: 1.23% (0.84–1.62%) per 10 µg/m ³ , lag 0-1 Range of individual city estimates: 0.90–1.97%	Estimates robust to adjustment in three cities – presented as plots in Fig. 2A in supplementary material (and as Fig 7 in HEI (2010)).	Excess risk: 0.55% (0.26–0.85) per 10 µg/m ³ PM ₁₀ Range of individual city estimates: 0.26–1.25%	Estimates attenuated and lost statistical significance after adjustment in three cities – presented as plots in Fig. 2B in supplementary material (and as Fig. 9 in HEI (2010)).	Estimates for NO ₂ were larger than those reported in Europe (Samoli et al. (2006)).
Chiusolo et al. (2011) 10 Italian cities (EpiAir) ≥ 35 years	Mean (24 hours): 26–66 µg/m ³	Not reported in the paper	Random effects estimate: 2.09% (0.96–3.24%) per 10 µg/m ³ NO ₂ , lag 0-5	Random effects estimate: 1.95% (0.50–3.43%) increase in risk per 10 µg/m ³ increase in NO ₂ (+PM ₁₀)	Not reported in the paper	Not reported in the paper	--
Chen et al. (2012b) 17 Chinese cities, (CAPES) All ages	Mean (24 hours): 26–67 µg/m ³ Max. (24 hours): 106–254 µg/m ³	NO ₂ :PM ₁₀ : 0.66	1.63% (1.09–2.17%) per 10 µg/m ³ , lag 0-1	1.28% (0.72–1.84%), lag 0-1	Reported in Chen et al. (2012a) : 0.35% (0.18–0.52%) per 10 µg/m ³ PM ₁₀	Reported in Chen et al. (2012a): 0.16% (0.00–0.32%) per 10 µg/m ³ PM ₁₀	--
Cardiovascular and/or cardiac mortality							
Samoli et al. (2006) 30 European cities (APHEA-2) All ages	Mean (1 hour max.): 46.2–154.8 µg/m ³	NO ₂ :BS: 0.11–0.78	Random effects estimate: 0.40% (0.29–0.52%) per 10 µg/m ³ NO ₂ , lag 0-1	Random effects estimate: 0.44% (0.31–0.58%) (+BS)	Not reported in the paper	Not reported in the paper	Fixed effect: 0.44% (0.31–0.58%) NO ₂ (+BS)
		NO ₂ :PM ₁₀ : 0.11–0.69		Random effects estimate: 0.35% (0.21–0.50%) (+PM ₁₀)			Fixed effect: 0.35% (0.24–0.45%) NO ₂ (+PM ₁₀)

Reference, study location, age group	NO ₂ level	Correlation with PM	NO ₂ estimate (95% CI)	NO ₂ + PM estimate (95% CI)	PM estimate (95% CI)	PM + NO ₂ estimate (95% CI)	Comments
Wong et al. (2008) 4 cities: 3 Chinese and 1 Thai (PAPA) All ages	Mean (24 hours): 44.7– 66.6 µg/m ³	NO ₂ :PM ₁₀ : 0.71–0.85	Excess risk: 1.36% (0.89– 1.82%) per 10 µg/m ³ , lag 0-1 Range of individual city estimates: 1.01–2.12%	Estimates robust to adjustment in three cities – presented as plots in Fig. 2A in supplementary material (and as Fig. 7 in HEI (2010)).	Excess risk: 0.58% (0.22– 0.93%) per 10µg/m ³ PM ₁₀ . Range of individual city estimates: 0.27–90%	Estimates attenuated and lost statistical significance after adjustment in three cities – presented as plots in Fig. 2B in supplementary material (and as Fig. 9 in HEI (2010)).	--
Chiusolo et al. (2011) 10 Italian cities (EpiAir) ≥ 35 years	Mean (24 hours): 26–66 µg/m ³	Not reported in the paper	Random effects estimate: 2.63% (1.53–3.75%) increase in the risk per 10 µg/m ³ in NO ₂ , lag 0-5	Random effects estimate: 2.58% (1.05–4.13%) increase in risk per 10 µg/m ³ increase in NO ₂ (+PM ₁₀)	Not reported in the paper	Not reported in the paper	--
Chen et al. (2012b) 17 Chinese cities, (CAPES) All ages	Mean (24 hours): 26–67 µg/m ³ Max. (24 hours): 106–254 µg/m ³	NO ₂ :PM ₁₀ : 0.66	1.80% (1.00– 2.59%) per 10 µg/m ³ , lag0-1	1.19% (0.30– 2.08%) per 10 µg/m ³	Reported in Chen et al. (2012a): 0.44% (0.23– 0.64%) per 10 µg/m ³ PM ₁₀	Reported in Chen et al. (2012a): 0.23% (0.03– 0.43%) per 10 µg/m ³ PM ₁₀	--
Respiratory mortality							
Samoli et al. (2006) 30 European cities (APHEA-2) All ages	Mean (1 hour max.): 46.2– 154.8 µg/m ³	NO ₂ :BS: 0.11–0.78	Random effects estimate: 0.38% (0.17–0.58%) per 10 µg/m ³ NO ₂ , lag 0-1	Random effects estimate: 0.26% (-0.12–0.65%) (+BS)	Not reported in the paper	Not reported in the paper	Fixed effect: 0.28% (-0.02–0.58%) NO ₂ (+BS)
		NO ₂ :PM ₁₀ : 0.11–0.69		Random effects estimate: 0.37% (0.08–0.67%) (+PM ₁₀)			Fixed effect: 0.37% (0.13–0.61%) NO ₂ (+PM ₁₀)

Reference, study location, age group	NO ₂ level	Correlation with PM	NO ₂ estimate (95% CI)	NO ₂ + PM estimate (95% CI)	PM estimate (95% CI)	PM + NO ₂ estimate (95% CI)	Comments
Wong et al., 2008 4 cities: 3 Chinese and 1 Thai city (PAPA) All ages	Mean (24 hours): 44.7– 66.6 µg/m ³	NO ₂ :PM ₁₀ : 0.71–0.85	Excess risk: 1.48% (0.68– 2.22%) per 10 µg/m ³ , lag 0-1 Range of individual city estimates: 1.05–3.68%	Estimates attenuated in some cities and became insignificant – presented in paper as plots in Fig. 2A in supplementary material (and as Fig. 7 in HEI (2010))	Excess risk: 0.62% (0.22– 1.02%) per 10 µg/m ³ PM ₁₀ . Range of individual city estimates: 0.27–1.01%	Estimates attenuated and, in all cities, were statistically insignificant following adjustment – presented as plots in Fig. 2B in supplementary material (and as Fig. 9 in HEI (2010)).	--
Chiusolo et al., (2011) 10 Italian cities (EpiAir) ≥ 35 years	Mean (24 hours): 26–66 µg/m ³	Not reported in the paper	Random effects estimate: 3.48% (0.75–6.29%) increase in the risk per 10 µg/m ³ NO ₂ , lag 0-5	Random effects estimate: 3.39% (0.77–6.08%) increase in risk per 10 µg/m ³ NO ₂ (+PM ₁₀)	Not reported in the paper	Not reported in the paper	--
Chen et al., 2012b 17 Chinese cities, (CAPES) All ages	Mean (24 hours): 26–67 µg/m ³ Max. (24 hours):106– 254 µg/m ³	NO ₂ :PM ₁₀ : 0.66	2.52% (1.44– 3.59%) per 10 µg/m ³ , lag 0-1	1.75% (0.76– 2.75%) per 10 µg/m ³	Reported in Chen et al. (2012a): 0.56% (0.31– 0.81%) per 10 µg/m ³ PM ₁₀	Reported in Chen et al. (2012a): 0.24% (0.00– 0.49%) per 10 µg/m ³ PM ₁₀	--

BS: black smoke; CO: carbon monoxide; O₃: ozone

Hospital admissions and emergency room visits

Papers on hospital admissions for various diagnoses, published since the 2005 global update of the WHO air quality guidelines, have been identified (an overview of which is given in Table 5). Only studies of hospitalization or emergency room visits for respiratory (all-respiratory, asthma and chronic obstructive pulmonary disease) and cardiovascular and/or cardiac diagnoses have been considered. Many of the new papers have been subject to extensive review – for example Anderson et al, 2007; CARB, 2007; EPA, 2008b) – and therefore have not been reviewed individually. Only studies published since (or not included in) the most recent review – that is, by the EPA (2008b) – are discussed below. A list of all time-series references on NO₂, including those on hospital admissions and emergency room visits, is available upon request.

Respiratory hospital admissions and emergency room visits

All respiratory diagnoses and asthma

In the 2005 global update of the WHO air quality guidelines, WHO concluded that the evidence suggested an effect of NO₂ on respiratory hospital admissions and emergency room visits, especially for asthma.

This review consists of 41 new papers on respiratory (all-respiratory, asthma and chronic obstructive pulmonary disease) hospital admissions and emergency room visits. Four papers, based on multicity studies, were available (Eilstein et al., 2004; Barnett et al., 2005; Simpson et al., 2005b; Colais et al., 2009).

In 2008, the EPA concluded that there were positive short-term associations of NO₂ with increased respiratory hospital admissions and emergency department visits, especially for asthma. The associations were noted to be particularly consistent among children and older adults (more than 65 years of age) for all respiratory diagnoses, and among children and all age groups for asthma admissions. The associations with NO₂ were regarded as being generally robust to adjustments for particles and gaseous pollutants. Many of the studies considered in the EPA review used a 24-hour measure of exposure, with a number of them reporting mean concentrations of NO₂ within the range of 5.6–94.0 µg/m³ (maximums of 52.6–154.2 µg/m³). Similar conclusions were also reported by the California Environmental Protection Agency Air Resources Board (CARB, 2007). The meta-analysis of single-pollutant model estimates by Anderson et al. (2007) supports the conclusions by the EPA and CARB, reporting positive and mainly statistically significant overall estimates (percentage increase per 10 µg/m³) for respiratory hospital admissions and 24-hour concentrations: 1.80% (95% CI: 1.15–2.45%), 0.82% (95% CI: 0.35–1.29), 1.47% (95% CI: 0.10–2.87), and 0.48% (95% CI: -0.35–1.31) for all ages, children, young adults, and the elderly, respectively. Overall effect estimates for asthma hospital admissions were 1.37% (95% CI: 0.59–2.15) and 2.92% (95% CI: 1.15–4.72) for 24-hour average NO₂ in all ages and children, respectively. Pooled estimates for these health outcomes for maximum 1-hour average concentrations of NO₂ were smaller than those for 24-hour average concentrations (Anderson et al., 2007).

Papers published since (or not considered in) the EPA's 2008 review also reported positive (though not always statistically significant) single-pollutant associations for hospital admissions and emergency room visits for: (a) asthma (Bell, Levy & Lin (2008), Colais et al., 2009; Giovannini et al., 2010; Halonen et al., 2008; Jalaludin et al., 2008; Samoli et al., 2011a; Szyszkowicz, 2008; Ueda, Nitta & Odajima, 2010; Villeneuve et al., 2007) and

(b) respiratory causes (Colais et al., 2009; Eilstein et al., 2004; Faustini et al., 2013; Granados-Canal et al., 2005; Giovannini et al., 2010; Jayaraman & Nidhi, 2008; Thach et al., 2010; Vigotti et al., 2010).⁸ Serinelli et al. (2010) and Kim, Kim & Kim (2006) reported negative associations between NO₂ and respiratory and asthma hospital admissions, respectively; Kim, Kim & Kim (2006) also found a positive association between NO₂ and emergency visits for asthma. The associations reported in the new papers published since EPA (2008b) are based largely on 24-hour average concentrations of NO₂ measured at urban background sites. Very few studies used 1-hour measures.

Where confounding by co-pollutants was assessed in the studies since the EPA (2008b) review, some robustness to adjustment was demonstrated for these respiratory health outcomes (Giovannini et al., 2010; Ueda, Nitta & Odajima, 2010; Halonen et al., 2008; Jalaludin et al., 2008; Jayaraman & Nidhi, 2008; Villeneuve et al., 2007). For example, Halonen et al. (2008) found that NO₂ was a strong and independent predictor of asthma emergency room visits in children in Finland. The authors examined a range of single day lags from lag 0 to lag 5, and found that for lags of 3–5 days, all particle fractions below 250 nm, NO₂ and carbon monoxide were each associated with asthma emergency room visits in children. In two-pollutant model analyses, the association with ultrafine particles (for an interquartile range increase in concentration) was removed after adjustment for NO₂ – from 6.6% (95% CI: 2.34–11.00%) to -0.89% (95% CI: -6.11–4.62%) at lag 4. Although the NO₂ estimates were not shown in the paper, the authors reported that they were not sensitive to adjustment for other pollutants (PM_{2.5}, nucleation and Aitken mode particle sizes,⁹ coarse particles and carbon monoxide). These pollutants were not too highly correlated: the highest correlation (0.65) was between NO₂ and ultrafine particles. Giovannini et al. (2010) reported estimates for asthma and all-respiratory conditions in children that, respectively, increased (from a RR of 1.002 (1.000–1.004) to a RR of 1.004 (0.993–1.015)) or were negligibly affected (from RR of 1.009 (1.001–1.017) to 1.008 (0.999–1.016)) by adjustment for carbon monoxide. Ueda, Nitta & Odajima (2010) also reported an increase in the estimate for asthma hospitalisation in children (from an odds ratio of 1.112 to an odds ratio of 1.128) following adjustment in a multi-pollutant model, though this lost statistical significance.

Iskandar et al. (2012) also reported statistically significant associations of NO₂ with asthma hospital admissions in children in Copenhagen¹⁰ following adjustment for several PM metrics. The association was slightly attenuated and remained statistically significant following adjustment for PM₁₀; it increased following adjustment for PM_{2.5} and ultrafine particles; but was reduced and lost statistical significance following adjustment for nitrogen oxides. With the exception of ultrafine particles, associations with PM₁₀ and PM_{2.5} and asthma hospital admissions in children remained positive (though attenuated) and statistically significant following adjustment for NO₂. Leitte et al. (2011) examined relationships between NO₂ and various particle sizes and respiratory emergency room visits in Beijing, China. In two-pollutant model analyses, the most consistent associations were found with NO₂ (adjusted for PM₁₀).

⁸ Faustini et al. (2013) was published after the last update of APED in April 2011 and is not presented in Table 5. In two-pollutant models, with both NO₂ and PM₁₀, the associations for both pollutants for respiratory hospital admissions remained but were lower and not statistically significant.

⁹ Particle definitions provided by Halonen et al. (2008): nucleation mode (< 0.03 µm), Aitken mode (0.03–0.1 µm), ultrafine particles (< 0.1 µm), accumulation (0.1–0.29 µm) mode, coarse particles (PM₁₀–PM_{2.5}).

¹⁰ Iskandar et al. (2012) and Leitte et al. (2011) were published after the last update of APED in April 2011 and are not presented in Table 5.

Results from APHEA-2 for PM₁₀ and hospital admissions show that after adjustment for NO₂, the estimate for asthma in 0–14-year-olds is reduced from a statistically significant increase of 1.2% to 0.1% (95% CI: -0.8–1.0%) per 10 µg/m³ PM₁₀ (Atkinson et al., 2001); similar findings for the 15–64-year age group were reported (reduced from 1.1% to 0.4% (95% CI: -0.5–1.3%). These findings suggest that NO₂ had a stronger association with asthma admissions than did PM₁₀.

Not all studies demonstrated robustness. For example, Samoli et al. (2011a) reported a positive (1.10%, per 10 µg/m³ increase in NO₂), but a statistically insignificant single-pollutant model association for childhood asthma admissions in Athens. This association was reduced after controlling for PM₁₀ (estimate reduced to 0.54%) and SO₂ (estimate reduced to -0.78%) in two-pollutant models. Corresponding results for PM₁₀ showed a small reduction in the central estimate (from 2.54% to 2.28%) and loss of statistical significance after adjustment for NO₂. This was a small study, covering 3 years with a median of just two asthma admissions daily. Chen et al. (2010b) did not use two-pollutant models to investigate relationships with respiratory hospital admissions, as no statistically significant associations between NO₂ (or PM₁₀ and SO₂) and respiratory hospital admission were found in single-pollutant models.

Chronic obstructive pulmonary disease

A total of 13 papers on hospital admissions for chronic obstructive pulmonary disease are available for review. (It should be noted that some of these analysed chronic obstructive pulmonary disease and asthma together.) Eight of the papers formed part of the EPA's 2008 review, in which they concluded that the limited evidence did not support a relationship between NO₂ and admissions for chronic obstructive pulmonary disease. The few remaining papers reported positive and statistically significant associations (Sauerzapf, Jones & Cross, 2009; Thach et al., 2010; Colais et al., 2009), or positive (many insignificant) or negative associations (Halonen et al., 2008; 2009) between NO₂ and chronic obstructive pulmonary disease admissions or emergency room visits. These associations were based on single-pollutant models.

Overall, for respiratory outcomes in general, the new studies continue to provide evidence of short-term associations between NO₂ and respiratory hospital admissions and emergency room visits, especially for asthma. Many studies have demonstrated that these associations are not confounded by co-pollutants, including PM₁₀ and common gaseous pollutants typically used in two-pollutant and/or multipollutant model analyses. The few data available do not allow firm conclusions to be made about the robustness of these associations to adjustment for ultrafine particles.

Cardiovascular and/or cardiac hospital admissions and emergency room visits

Twenty-two papers on hospital admissions or emergency room visits for cardiovascular and/or cardiac diagnoses (mainly in all ages and the elderly) formed part of this review. The EPA (2008b) reviewed 12 of these, with 10 reporting estimates from two-pollutant and/or multipollutant models. In 2008, the EPA concluded that while positive short-term associations between NO₂ and hospital admissions or emergency visits to hospital for cardiovascular-related disorders were identified (at mean 24-hour concentrations in the range 27.6–75.2 µg/m³), most of these were diminished in multipollutant models that also contained carbon monoxide and PM. The 2005 global update of the WHO air quality guidelines concluded that, although positive associations between NO₂ and admissions or visits to

hospital for cardiovascular and/or cardiac diagnoses had been reported, drawing conclusions about the nature of the relationship was made less clear, since controlling for other pollutants at times lowered the effect estimates and at other times made them lose statistical significance.

The new studies published since (or not considered by) the EPA continue to show positive single-pollutant model associations: Eilstein et al. (2004) in nine French cities; Cakmak, Dales & Judek (2006a) in ten Canadian cities; Larrieu et al. (2007) in eight French cities; Chan et al. (2008) in Taipei, Taiwan, Province of China; Lefranc et al. (2009) in eight French cities; Colais et al. (2009) in nine Italian cities; and Alves, Scotto & Freitas (2010) in Lisbon, Portugal. Although Serinelli et al. (2010) also reported positive associations between NO₂ and cardiac hospital admissions for several lagged models, these were all statistically insignificant.

Only three of the new studies published since (or not considered by) the EPA review used two-pollutant and/or multipollutant models. A multicity Canadian study, by Cakmak, Dales & Judek (2006a) reported a positive and statistically significant association for cardiac hospital admissions (5.9% (95% CI: 3.2–8.6%), for a 40.23 µg/m³ concentration change) with NO₂ after adjustment for carbon monoxide, SO₂ and ozone. Using data from 58 urban counties in the United States for 1999–2005, Bell et al. (2009b) found a 1.30% (95% CI: 0.87–1.73%) increase in cardiovascular hospital admissions in the elderly per 17.7 µg/m³ interquartile range increase in NO₂ after adjustment for carbon monoxide and PM_{2.5}. The estimate for 9.8 µg/m³ interquartile range increase in PM_{2.5} was -0.18% (95% CI: -0.49–0.14%) after adjustment for NO₂ and carbon monoxide. Chen et al. (2010b) also reported a robust association for cardiovascular hospital admissions following adjustment for PM₁₀ (from 0.80% (95% CI: 0.10–1.49%) to 0.71% (95% CI: 0.00–1.41%)) but not for SO₂ (reduced to 0.28% (95% CI: -0.76–1.32%)).

In summary, the new evidence continues to show positive associations between NO₂ and hospital admissions and emergency room visits for cardiovascular and/or cardiac diagnoses. Given the mixed findings from the studies using (or reviewing) two-pollutant and/or multipollutant models published since the 2005 global update of the WHO air quality guidelines and given that none of the short-term studies of other cardiovascular-related endpoints – for example, heart failure, ischaemic heart disease – have been reviewed, it is difficult to comment further on the nature of the relationship between NO₂ and hospital admissions or visits for cardiovascular and/or cardiac diseases. The evidence for positive associations could allow quantitative exploration in sensitivity analyses (see Question C4).

1.2 Panel studies

The short-term effects of NO₂ on respiratory health in children with asthma were recently reviewed (Weinmayr et al., 2010). The review is based on 36 panel studies published 1992–2006, of which 14 are from the Pollution Effects on Asthmatic Children in Europe (PEACE) project, all from 1998. In the meta-analysis of these studies, NO₂ showed statistically significant associations with asthma symptoms when considering all possible lags, but not when similar lags (0, 1 or 0–1) were evaluated from each study. The association with cough was statistically significant, but only when the PEACE studies were not considered (The PEACE study was negative. On the one hand it is the only multicentre study with a uniform protocol; on the other hand, concerns have been raised that the results were influenced by an influenza epidemic during the relatively short observation period (2 months)). The estimated effect on peak expiratory flow was statistically insignificant.

A PubMed search identified 11 new articles: 6 from the Americas (Sarnat et al., 2012; O'Connor et al., 2008; Escamilla-Nuñez et al., 2008; Liu et al., 2009; Castro et al., 2009; Dales et al., 2009), 2 from Europe (Andersen et al., 2008b; Coneus & Spiess, 2012), and 3 from Asia (Min et al., 2008; Yamazaki et al., 2011; Ma et al., 2008). All, except two, studies investigated school-aged asthmatic and/or symptomatic children, while the remaining two considered infants and toddlers (Andersen et al. 2008b; Coneus & Spiess, 2012). Most of the studies observed positive associations between short-term exposure to NO₂ (or nitrogen oxides) for different lags and respiratory symptoms, such as coughing and wheezing (O'Connor et al., 2008; Escamilla-Nuñez et al., 2008; Andersen et al., 2008b), as well as for exhaled nitric oxide (Sarnat et al., 2012) and also for pulmonary function decrease (O'Connor et al., 2008; Liu et al., 2009; Castro et al., 2009; Dales et al. 2009; Min et al., 2008; Yamazaki et al., 2011; Ma et al., 2008) in children, although not all of them were statistically significant (Dales et al., 2009). One article reported numerical data only for PM (Min et al., 2008).

The largest of these studies included 861 children with asthma from seven inner-city communities in the United States (O'Connor et al., 2008). A difference of 20 ppb in the 5-day average concentrations of NO₂ was associated with an odds ratio (OR) of 1.23 (95% CI: 1.05–1.44), for having a peak expiratory flow less than 90% of personal best. Similar risk elevations were found for decreased FEV₁, cough, night-time asthma, slow play and school absenteeism. Multipollutant models showed independent effects for NO₂ after adjustment for ozone and PM_{2.5} for most of these end-points.

In addition, some panel studies were published earlier, but were not included in the meta-analysis mentioned above (Svendsen et al., 2007; Delfino et al., 2006; Trenga et al., 2006; Moshhammer et al., 2006; Mar et al., 2005; Rabinovitch et al., 2004; Ranzi et al., 2004; Boezen et al., 1999). These studies are not reviewed here, but are cited to illustrate, combined with the points made earlier, that a new combined analysis would contribute to a more precise quantitative estimation of the effects of short-term fluctuations in outdoor NO₂ concentrations on changes in pulmonary function and respiratory symptoms in asthmatic children, given the increased number of studies available. This might be performed by enlarging the existing review (Weinmayr et al., 2010) with the recently published panel studies. A new combined analysis could also consider panel studies performed on indoor exposure and respiratory effects – for example, Marks et al. (2010).

This section has concentrated on panel studies of respiratory health in children. There are also studies on chronic obstructive pulmonary disease in adults (Peacock et al. (2011) found effects of NO₂ weakened by control for PM₁₀) and on cardiovascular end-points. Panel studies with end-points relevant to mechanistic questions are discussed in the toxicology section.

Of particular interest is a recent study conducted in the Netherlands that attempted to isolate which component of the ambient aerosol could be related to various acute response end-points in subjects exposed at five separate microenvironments, of contrasting source profile: an underground train station, two traffic sites, a farm and an urban background site. To date, only the results of the associations with respiratory end-points have been published, but this data suggested that interquartile increases in particle number concentration and NO₂ were related to decreased lung function (FVC and FEV₁) – associations that were insensitive to adjustment for other gaseous pollutants and an extensive range of PM metrics, including

black carbon, particle number concentration, oxidative potential and transition metals (Strak et al., 2012).

1.3 Chamber studies

Since 2005, the literature on human exposure to NO₂ has undergone a number of systematic reviews, as part of the EPA integrated scientific assessment for oxides of nitrogen (EPA, 2008b) and later by Hesterberg et al. (2009) and Goodman J et al. (2009). The human chamber study evidence was also reviewed by the California Environmental Protection Agency Air Resources Board (CARB, 2007) in their assessment of the California NO₂ standard. Since the publication of these reviews, limited NO₂ chamber studies that address lung function and airway inflammation have been performed, and two studies that address cardiovascular end-points have been published (Langrish et al., 2010; Scaife et al., 2012). Therefore, the conclusions that arise from these reviews remain valid for consideration of the current NO₂ standards.

The human chamber studies generally only address a single pollutant, but this can be helpful when it is unclear whether the health effects reported in the so-called real world are related to the pollutant itself, or a mixture of pollutants for which NO₂ serves as a surrogate. This is particularly true for NO₂, where there is an apparent mismatch between the human chamber exposure data (with mixed evidence of inflammation or impaired lung function between 0.26 ppm and 0.60 ppm) and the population-based epidemiology (with effects reported at lower concentrations within the ambient range). The results from the chamber studies are therefore useful in determining whether NO₂ should be considered toxic to the population in its own right or should be considered a tracer for local source emissions – that is, traffic in urban areas.

Human clinical studies generally examine healthy subjects, or patients (asthmatics, chronic obstructive pulmonary disease patients, allergic rhinitis patients, and patients undergoing rehabilitation following cardiac events) with relatively stable symptoms exposed to a single NO₂ concentration for durations of 1–6 hours. Results are generally compared against a control air exposure, with a range of end-points examined, including lung function, exhaled gases, airway inflammation (either by bronchoscopy or by induced sputum) and airway hyperresponsiveness. The results observed from these acute exposures are usually transient and, though often statistically significant, are seldom clinically so. Healthy subjects have been exposed acutely to NO₂ concentrations that range from 0.3 ppm to 2.0 ppm (1–4 hours); sensitive subgroups, including asthmatics and chronic obstructive pulmonary disease patients have been exposed to 0.26–1.00 ppm. Above 1 ppm, clear evidence of inflammation has been observed in healthy subjects in a number of studies (Helleday et al., 1995; Devlin et al., 1999; Pathmanathan et al., 2003; Blomberg et al., 1999), but the picture is less established at concentrations between 0.2 ppm and 1.0 ppm (Vagaggini et al., 1996; Jörres et al., 1995; Gong et al., 2005; Frampton et al., 2002; Riedl et al., 2012), partially because of inconsistent responses in the varying end-points examined.

A number of studies have suggested that NO₂ can augment allergen-induced inflammation in asthmatics (Barck et al., 2002, 2005) following short (15–30 minutes) consecutive day exposures at relatively low concentrations (0.26 ppm). However other studies at comparable NO₂ concentrations, but at a higher total dose (0.4 ppm for 3 hours), have failed to demonstrate a similar enhancement of airway inflammation or a reduced house-dust-mite allergen provocation dose in allergic asthmatics (Witten et al., 2005). Similarly, Vagaggini et al. (1996) were unable to demonstrate NO₂-induced upper airway inflammation in mild

asthmatics, by nasal lavage and induced sputum 2 hours after an exposure to 0.3 ppm NO₂ for 1 hour. The evidence for inflammation in asthmatics exposed to NO₂ concentrations near environmental concentrations is therefore ambiguous.

Few studies have reported acute lung function changes near the current guideline concentration value (Bauer et al., 1986; Jörres et al., 1995) in the absence of a specific or nonspecific challenge (reviewed in Hesterberg et al., 2009; EPA, 2008b). In those studies that reported decrements, exposure concentrations were high (more than 1 ppm) and the magnitude of the observed changes was unlikely to be of clinical significance (Blomberg et al., 1999).

The reported effects of NO₂ on nonspecific and specific airway hyperresponsiveness have been reviewed in detail in the EPA integrated science assessment (2008b), as well as by Goodman J et al. (2009) and Hesterberg et al. (2009). In healthy individuals, small increases in nonspecific airway hyperresponsiveness have been reported following short-term (1–3 hour) exposure to NO₂ in the range 1.5–2.0 ppm (Mohsenin, 1987; Frampton et al., 1989). In asthmatics, the data on nonspecific hyperresponsiveness to NO₂ suggests a sensitizing effect between 0.2 ppm and 0.6 ppm, though the responses, where significant, were small and unlikely to be of clinical significance (Bylin et al., 1985; Mohsenin, 1987; Strand et al., 1996). A limited number of studies have evaluated airway hyperresponsiveness in asthmatics at multiple NO₂ concentrations, and the results of these studies do not support a clear concentration–response relationship between 0.1 ppm and 0.5 ppm (Bylin et al., 1988; Roger et al., 1990; Tunnicliffe, Burge & Ayres, 1994). It should be noted that, in all of the studies cited, a range of responses were observed; and in many studies, subgroups of responders were identified. Given that chamber studies by their very nature rely on typically small numbers of healthy volunteers, or clinically stable patients, it is likely that they may underestimate the responses of sensitive subgroups within the population, especially in relation to disease severity.

Langrish et al. (2010) failed to demonstrate vascular dysfunction (vascular vasomotor or fibrinolytic function) in healthy volunteers exposed to 4 ppm NO₂ or filtered air for 1 hour. This is an important paper, as this result contrasts markedly with the group's previous findings using diesel exhaust containing high concentrations of NO₂ (Mills et al., 2007). A subsequent paper, examining the vascular and prothrombic effects of diesel exhaust (300 µg/m³ for 1 hour), with and without inclusion of a particle trap, demonstrated that a reduction of particle number and mass concentration, in the absence of changes in nitrogen oxides, was associated with reduced adverse cardiovascular outcomes (Lucking et al., 2011). This was interpreted as strongly supporting the view that fine particles, and not NO₂, were driving the previously reported cardiovascular effects, especially as NO₂ concentrations increased almost five-fold with the particle trap. Further evidence, suggesting the absence of an acute cardiovascular effect of NO₂, was reported by Scaife et al. (2012). In this study they found no significant changes in heart variability parameters in 18 heart bypass and myocardial infarction patients following exposure to 400 ppb NO₂ for 1 hour.

1.4 Toxicological studies on short-term exposure (hours to days)

The WHO Regional Office for Europe indoor air quality guideline (2010) noted that acute exposures (hours) in the range of 0.04–1.0 ppm were rarely observed to cause effects in animals. The California Environmental Protection Agency Air Resources Board (CARB,

2007) noted acute effects (hours) in rats and mice at 0.2–0.8 ppm NO₂ (increased mast cells, quoted from Hayashi & Kohno (1985) in CARB, 2007)*¹¹ and increased synthesis of the carcinogen dimethylnitrosamine (Iqbal, Dahl & Epstein, 1981)* at 0.2 ppm. Also, there were: effects on liver detoxification enzymes at 0.25 ppm (Miller et al., 1980)*; effects on macrophages at 0.3–0.5 ppm (e.g. Robison et al., 1993)*; and increased bronchiolar proliferation at 0.8 ppm (Barth et al., 1994)*. The EPA (2008b) also highlighted the study by Barth et al. (1994). The effects at 0.2–0.25 ppm are harder to interpret (the mast cells may not have been degranulating, dimethylnitrosamine synthesis relied on an additional administered precursor and the effect on liver enzymes may not be adverse), but it is clear that the effects are adverse above 0.3 ppm. Tables in these reports quote other studies that report acute no effect levels from 0.4 ppm to 0.8 ppm.

A literature search, and literature abstracts already held from 2008 onwards (the literature cut-off for WHO Regional Office for Europe (2010)),¹² did not indicate any animal studies with short-term exposure to NO₂ alone that would change the CARB (2007) or EPA (2008b) view. Urea selective catalytic reduction-treated diesel engine emissions (0.78 ppm NO₂ and dilutions) were generally less toxic to rat lungs than conventional diesel engine emissions (0.31 ppm NO₂ and dilutions), for various endpoints over durations of 1, 3 or 7 days. However, there were differences in the nature of the oxidative stress produced with either increases in 8-hydroxy-2-deoxyguanosine with conventional diesel engine emissions, or increases in haemoxygenase-1 mRNA expression with urea selective catalytic reduction-treated diesel engine emissions (Tsukue et al., 2010). The latter suggests oxidative stress related to NO₂, but is not conclusive, given the mixture of constituents present.

Using exposures lasting from hours to days, recent mechanistic animal studies show: protein S-glutathionylation in the lung at 25 ppm NO₂ (Aesif et al., 2009); a decrease in aggregating activity of surfactant-protein D at 10 ppm or 20 ppm (Matalon et al., 2009); and increases in markers of oxidative stress, endothelial dysfunction, inflammation and apoptosis in the hearts of rats from exposures of 2.7 ppm to 10.6 ppm (Li H et al., 2011). Zhu et al. (2012) found that 2.6 ppm NO₂ delayed recovery from stroke (slowed reduction in infarct volume) in a rat stroke model and increased behavioural deficits. Dose-related endothelial and inflammatory responses were also found in the range 2.6–10.6 ppm. Channell et al. (2012) found that plasma from healthy adults exposed to 0.5 ppm NO₂ for 2 hours was able to activate cultured primary human coronary endothelial cells. This suggested that a circulating factor was mediating, at least in part, the endothelial response that may underly the cardiovascular epidemiological findings. One study in mice (Alberg et al., 2011) found no increased sensitization to intranasal ovalbumin at 5 ppm or 25 ppm NO₂ when diesel exhaust particles did show an increase, whereas another study in mice (Hodgkins et al., 2010) at 10 ppm NO₂ showed sensitization to inhaled ovalbumin due to increased antigen uptake by antigen-presenting cells. A study in mice suggested that effects in the lung due to 20 ppm NO₂ for 10 days are worse with a small increase in vitamin C dose than with a large increase (Zhang et al., 2010), perhaps due to vitamin C increasing NO₂ absorption into the epithelial lining fluid (Enami, Hoffmann & Colussi, 2009). All these concentrations (apart from Channell et al., 2012) are far in excess of the ambient concentrations linked to health effects in population studies, and the studies are not designed to show whether the mechanisms extend down to lower concentrations – that is, the mechanisms may or may not be relevant.

¹¹ Studies followed by asterisks (*) are older studies not referenced in earlier guidelines.

¹² Literature abstracting service was provided by the Institute of Environment and Health at Cranfield until 2009; it was funded by the United Kingdom Department of Health.

Recent studies indicate that the NO_2 radical can be directly involved in nitration of tyrosines (Surmeli et al., 2010, for example) and also that it causes a nitration-dependent *cis-trans*-isomerization to *trans*-arachidonic acid (linked to microvascular injury), described by the authors as a characteristic process for NO_2 (Balazy & Chemtob, 2008). This is not just relevant to the lung. While NO_2 itself is not absorbed systemically, as it is likely to react first, its reaction products, nitrite and nitrate ions, are found in the blood after NO_2 inhalation (Saul & Archer, 1983). Nitrite and nitrate anions in the blood are now regarded as carriers of nitric oxide (Lundberg, Weitzberg & Gladwin, 2008; Lundberg & Weitzberg, 2010; Weitzberg, Hezel & Lundberg, 2010).

The cycle whereby nitrate is excreted into the saliva and reduced to nitrite by oral bacteria and then converted to nitric oxide in the stomach or in the blood and tissues, after absorption of nitrite, may have a physiological role (to ensure nitric oxide production for vasodilation under hypoxic conditions when oxygen dependent nitric oxide synthases may fail), but may also have adverse consequences (Panesar, 2008). Nitrite can also lead to the NO_2 radical via peroxidase catalysed oxidation with hydrogen peroxide, via formation of nitrous acid, which dissociates to nitric oxide and NO_2 , via formation of peroxynitrite from nitric oxide and superoxide and subsequent breakdown to the NO_2 and hydroxyl radicals and, less commonly, direct oxidation of nitric oxide (d'Ischia et al., 2011; Signorelli et al., 2011). In other words, there is an indirect transfer of inhaled NO_2 to the NO_2 radical in tissues via reactive intermediates.

There is a great deal of literature on reactive nitrogen species (Abello et al., 2009; d'Ischia et al., 2011; Sugiura & Ichinose, 2011), including in literature on atherosclerosis (Upmacis, 2008). The review by Upmacis (2008) describes the occurrence of protein nitrotyrosine in atherosclerotic plaques and also in the bloodstream and describes an emerging view that this is a risk factor for cardiovascular disease. A major proportion of the nitrotyrosine is thought to come via nitric oxide from inducible nitric oxide synthase (induced under inflammatory conditions), but the source of the remainder is unknown. Nitrite and nitrate in the blood from NO_2 inhalation provides a potential link with this literature. Human beings exposed to 0.1 ppm NO_2 by inhalation have been inferred to form about 3.6 mg nitrite per day, more than the dietary intake of nitrite (Saul & Archer, 1983). More work is needed, however, to understand how significant any contribution of NO_2 inhalation to systemic nitrate stress might be in quantitative terms.

Although this is a section on toxicology, some epidemiological studies are considered here as they concentrate on mechanisms. They provide a potential link between the mechanisms in animal studies discussed above and mechanisms operating in human beings, although they lose the advantage of confident specificity for NO_2 . These studies have mostly addressed cardiovascular end-points: no effects on blood coagulation and inflammatory markers (Zuurbier et al., 2011b; Steinvil et al., 2008) or a non-significant increase (significant for sP-selectin) (Delfino et al., 2008); increases in brachial artery diameter and flow mediated dilatation (perhaps actually due to nitric oxide) (Williams et al., 2012); adverse effects on heart rate variability in heart disease patients (Zanobetti et al., 2010) and in cyclists (Weichenthal et al., 2011) (independent of PM metrics); a non-significant increase in the QT interval in electrocardiograms (significant in diabetics) (Baja et al., 2010); and an increase in lipoprotein-associated phospholipase A2 (linked to inflammation in atherosclerotic plaques) (Brüske et al., 2011).

2. Long-term guideline

2.1 Long-term epidemiological studies

Since the publication of the 2005 global update of the WHO air quality guidelines, a large number of new studies on long-term effects related to NO₂ and other traffic pollutants have been published. To prepare a response to the question on new evidence, systematic literature searches were performed for original articles published 2004 to April 2012 on long-term studies (cohort studies, cross-sectional studies, case-control studies) that investigated outdoor NO₂ exposure and mortality or diagnosed diseases or lung function. We did not look at other physiological markers and at birth outcomes, as it is not clear whether they are really consequences of long-term exposure, and there were too few studies meeting the criteria. The searches in the literature databases PubMed, ISI Web of Science and Ludok resulted in 160 publications: on mortality or specific death causes ($n = 37$); on lung function ($n = 34$); on incidence or prevalence of cardiovascular diseases ($n = 19$); on diabetes mellitus ($n = 6$); on asthma ($n = 46$); and on bronchitis ($n = 18$).

In addition, two review reports from the California Environmental Protection Agency Air Resources Board and the EPA published in 2007 and 2008, respectively, have been reviewed.

1. **Review of the California Ambient Air Quality Standard for NO₂, 2007.** The following recommendation was released for a NO₂ annual-average standard: establish a new annual average standard for NO₂ of 56 µg/m³ (0.030 ppm), not to be exceeded. It was based on evidence from epidemiological studies showing that long-term exposures (that is, one or more years) to NO₂ may lead to changes in lung function growth in children, symptoms in asthmatic children, and preterm birth (CARB, 2007).
2. **EPA integrated science assessment for oxides of nitrogen – health criteria, 2008.** This document rated the epidemiological and toxicological evidence, examining the effect of long-term exposure to NO₂ on respiratory morbidity, as suggestive, but not sufficient to infer a causal relationship. The document also rated the evidence on other morbidity or mortality as inadequate to infer the presence or absence of a causal relationship. It found the relationship between long-term exposure to NO₂ and mortality to be inconsistent. Furthermore, when associations were noted, they were not specific to NO₂, but also implicated PM and other traffic indicators.

Long-term studies generally investigate geographic differences in NO₂ exposure for a period of several years. The spatial distribution of NO₂ shows a high variation, as it varies mainly with traffic – the most important NO₂ source in European countries. Therefore, individual assessment of exposure is much more important than the assessment of more homogeneously distributed PM_{2.5} or (often) PM₁₀. So, the spatial resolution of the exposure assessment is crucial. In contrast to particle mass, black smoke (or black carbon) often shows a similar spatial distribution to NO₂. The answer to the question about whether long-term effects are due to NO₂ per se should ideally be based on studies that include NO₂ together with a particle mass indicator (on the one hand) and an indicator such as black carbon or ultrafine particles (on the other hand).

Some of the newly published studies were ecological in nature (lacking individual covariates) or did not give numerical results for NO₂; and some had been superseded by more recent analyses with more data and longer follow up. These studies were excluded. As an indicator of long-term traffic exhaust, 31 of the studies modelled exposure to NO₂ or nitrogen oxides

and did not include a particle measure (14 of them investigating asthma). In these cases, it is not possible to attribute the resulting effects to NO₂ per se, so they are not discussed in detail here. A total of 81 studies analysed NO₂ and a particle measure in parallel, most of them investigating mortality, asthma, or lung function.

Some of these studies will be highlighted below, according to the following criteria:

- cohort studies with individual follow-up, as their validity is higher than cross-sectional studies or studies based on so-called ecological units; and
- studies with a contemporary evaluation of a PM fraction, preferably PM_{2.5} or black carbon.

Meta-analyses that include studies with and without a contemporary evaluation of a PM fraction and with a comparison with PM are also highlighted. A tabulation of the full set of studies is available on request.

The following discussion focuses on respiratory health in children and long-term mortality studies, as these are the outcomes with the largest number of investigations and with results relevant to possible standard settings.

Long-term effects on lung function development in children

The database available for evaluating the relationship between lung function growth in children and long-term exposures to NO₂ has increased. Three large cohort studies have examined this relationship. The California-based Children's Health Study, examining exposure to various pollutants in children for an 8-year period in 12 communities, demonstrated deficits in lung function growth (Gauderman et al., 2004) (FVC, FEV₁, maximal mid-expiratory flow (MMEF)) for NO₂, PM_{2.5}, elemental carbon and acid vapour. The average NO₂ concentrations during the study period ranged from about 7.5 µg/m³ to 71.4 µg/m³ (4–38 ppb). The effects for NO₂ were generally greater than has been found for the other pollutants, although the authors recognize that, as for other studies, they could not discern independent effects of pollutants, because they came from common sources and there is a high degree of inter-correlation between them. A later publication of the Californian children cohort studies by Gauderman et al. (2007), including the results of a second cohort and a focus on traffic, provided almost the same estimates for FEV₁ and background NO₂. The estimate was not altered by inclusion of the traffic indicator in the model with NO₂ and vice versa.

Similar findings for lung function growth have also been observed across 10 areas in Mexico City (Rojas-Martinez et al., 2007), where the levels of pollution were rather high (study area means for 1996–1999 of: NO₂: 51–80 µg/m³; PM₁₀: 53–97 µg/m³). The effect of an interquartile range NO₂ exposure was slightly larger than that of the effect of PM₁₀ in both boys and girls, with similar results being found in two-pollutant models. In Oslo and Stockholm, Oftedal et al. (2008) and Schultz et al. (2012) reported that the lifetime (Oslo) or first year of life (Stockholm) exposure to NO₂ from traffic was associated with decreased lung function at 9–10 (Oslo) and 8 (Stockholm) years. Because of the high correlation with other air pollutants, the effects could not be separated with multipollutant models. Overall, the association with deficits in lung function growth in single-pollutant models noted in the 2005 global update of the WHO air quality guidelines has been confirmed even in cities with low concentrations, and there is now evidence for an effect independent of PM₁₀ and PM_{2.5} in

multipollutant models, at least in a city (Mexico city) with a range of NO₂ concentrations at the upper end of the concentration range in Europe (Cyrus et al., 2012).

Long term effects on asthma

All the cohort studies that examined asthma outcomes identified in the search and published up to 2010 were included in a recently conducted systematic review by Anderson, Favarato & Atkinson (2013b). This evaluated the effects of NO₂ and PM_{2.5} on the incidence of asthma and wheeze. Results for NO₂ from 13 studies, most conducted in Europe, showed an overall RR estimate of 1.09 (95% CI: 1.05–1.14) per 10 µg/m³, after correcting for the scaling of results for one of the studies (Anderson et al., 2012). The overall effect estimate of five studies that evaluated the association between PM_{2.5} and the incidence of asthma and wheeze was 1.16 (95% CI: 0.98–1.37) per 10 µg/m³ PM_{2.5}. Given the larger spatial variability of NO₂ in comparison with PM_{2.5} (a factor of 1.5–3.0), the effect estimate for NO₂ is comparable, if not larger, than that for PM_{2.5}.

Most of these studies had mean or median (usually annual average) values for NO₂ below 40 µg/m³, including some positive studies with the entire concentration range below 40 µg/m³ and some negative studies in locations with higher concentration ranges. But the significance of this for setting guidelines is lessened, as none of the constituent studies performed two-pollutant models with NO₂ and particles. The analysis of the California Children's Health Study (McConnell et al., 2010) on asthma incidence did perform multipollutant analyses but did not do a two-pollutant analysis for the fixed site (background) measurements of NO₂ and PM, because it did not find a significant association with PM. Instead, it modelled traffic exposure at school and at home, based on nitrogen oxide estimates from modelling in a three-factor model, together with NO₂ concentrations from central site monitoring. In this three-factor model, the effects of the centrally monitored NO₂ levels (16.4–60.7 µg/m³ (8.7–32.3 ppb), annual average) did not disappear fully, but were reduced to statistical insignificance when including traffic exhaust (estimated by nitrogen oxides) at home and at school. Traffic at school and at home remained significant after including the effects of central site NO₂. McConnell et al. (2010) attribute the main effects to traffic exhaust, but note that the lack of statistical significance of the positive association with central-site NO₂ controlled for traffic could be due to exposure misclassification.

After the online publication of the Anderson et al. (2013b) meta-analysis, four cohort studies on asthma incidence and long-term average concentrations of NO₂ were published and all provide support for an association with NO₂. Carlsten et al. (2011a) and Gruzieva et al. (2013) also studied particles (showing an effect for PM_{2.5}, but not for black carbon), but none of these evaluated two-pollutant models with NO₂ and PM (Carlsten et al., 2011a; Andersen et al., 2012b; Lee Y et al., 2012; Gruzieva et al., 2013).

The results of prevalence studies of asthma are less clear, as it is uncertain whether they represent a true long-term effect on incidence. We describe a meta-analysis of these studies here, as it is an important body of literature: the studies may include questions on lifetime asthma, and they may be a more suitable basis for quantifying the effects of traffic measures (as asthma can remit over time, and the meta-analysis of asthma incidence did not control for the duration of follow-up period, as it was intended only for hazard assessment). The meta-analyses on the period prevalence of asthma and wheezing during the study period and on lifetime asthma by the same authors (Anderson, Favarato & Atkinson, 2013a), both based on

nine studies with pollution gradients mainly between communities,¹³ did not show any relationship with NO₂ or other pollutants. The authors did not exclude an association between the close proximity of traffic pollution and asthma in highly susceptible individuals, which may be diluted in a whole-community study. There are also a range of cross-sectional studies that investigated within-community exposure contrasts, more representative of traffic pollution, which have not been reviewed here, but include many positive associations with NO₂, some of which are statistically significant. Three of the recent area studies on asthma prevalence included multipollutant models (Dong et al., 2011; Pan et al., 2010; Sahsuvaroglu et al., 2009). In the study by Dong et al. (2011), the associations were reduced from an OR of 1.19 (95% CI: 1.06–1.34) per 10 µg/m³ in males and an OR of 1.14 (95% CI: 0.99–1.30) in females to an OR of 0.97 for both sexes in a five-pollutant model. In Pan et al. (2010), the effect estimates for current asthma associated with NO₂ were strongly reduced and lost statistical significance in a three-pollutant model with total suspended particulates and SO₂ (total suspended particulates and NO₂ were correlated with $r = 0.6$). Sahsuvaroglu et al. (2009) investigated asthma prevalence in schoolchildren in Hamilton, Canada. Overall, there was no association of asthma with any pollutant. Asthma was only significantly associated with NO₂ estimated with a land use regression model in the subgroup of girls without hay fever. This association showed a larger estimate after including SO₂, ozone and PM₁₀ in the same model.

The only study of long-term exposure and respiratory symptoms reviewed for the 2005 global update of the WHO air quality guidelines that included multipollutant models was that by McConnell et al. (2003), as part of the California Children's Health Study. Due to the importance of multipollutant models to the question of whether NO₂ is having an effect per se and the discussion of this study in Question C4, the study is described again here. McConnell et al. (2003) investigated the associations between bronchitis symptoms in children with asthma and particles and gaseous pollutants over a period of four years – between the study communities and with yearly within-community variability of pollution. Across communities, symptoms were associated with PM_{2.5}, elemental carbon and NO₂, but as those pollutants were closely correlated, no consistent between-community effects were observed in two-pollutant models. In contrast, the within-community associations were stronger, and the associations of symptoms with the yearly variability of organic carbon and NO₂ were, in general, not confounded by other pollutants. The yearly variability was expressed as the annual deviation from the 4-year average and ranged from 2.1 µg/m³ to 24.1 µg/m³ (1.1–12.8 ppb) deviations from 4-year averages of 7.9–71.4 µg/m³ (4.2–38.0 ppb) NO₂. No other pollutants were significantly associated with an increase in symptoms in models that included organic carbon or NO₂ (McConnell et al., 2003).

McConnell et al were cautious to attribute the associations with organic carbon to diesel exhaust, because there were no associations with elemental carbon, also stemming from diesel engines. They did not expect NO₂ to show the strongest associations and suggested the possibility of a smaller error in the measurement of organic carbon and NO₂ than in that of other correlated pollutants as being potentially responsible for the effect. No study of quite this design has been published since 2004 but, in general, while studies have continued to report associations between NO₂ and respiratory symptoms, in most cases it is neither proven nor disproven that these associations are related to NO₂ per se. However, indirect evidence –

¹³ One study was published since 2004.

from short-term studies and long-term studies on lung function, which supports the plausibility that some of these effects are due to NO₂ – has increased.

Summary of mortality-related to long-term exposure

A total of 18 cohort studies and two case-control studies published since 2004 provide RR estimates for associations of natural mortality, cardiovascular and respiratory mortality or lung cancer with NO₂ and PM. With the exception of studies conducted in China, most investigations were conducted in areas where the average NO₂ levels were below 40 µg/m³. Not all of the studies presented correlations between NO₂ and other pollutants, but those that did indicated moderate to high correlations; in European studies, the correlation is typically greater than 0.80. We focus mainly on the four cohort studies with multipollutant models and the five European cohort studies that analysed NO₂ and a particle metric – but without estimating two-pollutant models – giving details also in Tables 7 and 8.

Table 7. Cohort studies with multipollutant models for NO₂ and a particle measure and mortality risk

Author(s), publication (year) and location	Study design, population size and age, and study year	Pollutants and mean exposure for NO ₂ (averaging time is for date range given)	Outcome measure(s)	Effect estimates (95% CI)	Remarks
Cesaroni et al. (2013) Italy	Registry cohort study 1 265 058 adults 30 years and older Follow-up: 2001–2010	Annual averages at address, for NO ₂ estimated with LUR model, for PM _{2.5} with dispersion model; distance to traffic, traffic intensity Mean NO ₂ exposure at address: 43.6 µg/m ³ IQR: 38.5–49.2 µg/m ³ Mean PM _{2.5} exposure: 23.0 µg/m ³ IQR: 20.3–26.0 µg/m ³	Nonaccidental mortality, mortality from CVD, cerebrovascular disease, respiratory disease and lung cancer Overall: 144 441 deaths	Single-pollutant models: For nonaccidental mortality: HR: 1.03 (95% CI: 1.02–1.04) per IQR of NO ₂ HR: 1.02 (95% CI: 1.02–1.03) per IQR of PM _{2.5} For CVD mortality: HR: 1.03 (95% CI: 1.02–1.04) per IQR of NO ₂ HR: 1.04 (95% CI: 1.03–1.05) per IQR of PM _{2.5} For respiratory mortality: HR: 1.03 (95% CI: 1.00–1.06) per IQR of NO ₂ ; HR: 1.01 (95% CI: 0.99–1.05) per IQR of PM _{2.5} For lung cancer mortality: HR: 1.04 (95% CI: 1.02–1.07) per IQR of NO ₂ HR: 1.03 (95% CI: 1.01–1.06) per IQR of PM _{2.5}	High correlation between NO ₂ and PM _{2.5} exposures (0.79). In two-pollutant models NO ₂ with PM _{2.5} , per 10 µg NO ₂ /µm ³ : HR: 1.02 (95% CI: 1.01–1.03), per 10 µg/m ³ of PM _{2.5} HR = 1.01 (95% CI: 0.99–1.02) No data for smoking, but authors assume no impact because of information from a subset of the cohort. Estimated associations with NO ₂ and PM _{2.5} were similar or slightly stronger for all outcomes when adjusted for pre-existent diabetes, hypertension and COPD (no adjusting for COPD in analyses of respiratory mortality).
Jerrett et al. (2011) United States	Cohort study 76 343 adults 30 years and older, and who were members of households with at least one individual 45 years of age or more. Follow-up: 1982–2000	Individual ozone, NO ₂ (years 1988–2002), PM ₁₀ , PM _{2.5} (years 1998–2002) at address estimated with IDW interpolation, LUR and BME interpolation of LUR residuals. Mean individual NO ₂ -exposure modelled with LUR: 23.1 SD: 16 µg/m ³ , 95th% percentile: 32.1 µg/m ³ , Max.: 41.2 µg/m ³ .	Total mortality, mortality from CVD, IHD, respiratory disease and lung cancer Overall: 20 432 deaths	Per IQR of PM _{2.5} (5.35 µg /m ³): HR for all-cause mortality: 1.04 HR for CVD mortality: 1.08 HR for IHD mortality: 1.14 Per IQR of NO ₂ (7.7 µg /m ³): HR for all-cause mortality: 1.03–1.05 (range of different models estimates) HR for CVD mortality: 1.07–1.08 HR for IHD mortality: 1.12–1.13 HR for lung cancer: 1.10–1.17 (in Jerrett et al. (2011):74 (Table 36), 94, 116, 117).	In two-pollutant models of NO ₂ with PM _{2.5} , both pollutants had significantly elevated effects on mortality from CVD and IHD, additionally NO ₂ effects on all cause and lung cancer mortality remained significantly elevated. Effect estimates for multipollutant results not given. Correlation of NO ₂ LUR and PM _{2.5} was between 0.35 and 0.55.

Author(s), publication (year) and location	Study design, population size and age, and study year	Pollutants and mean exposure for NO ₂ (averaging time is for date range given)	Outcome measure(s)	Effect estimates (95% CI)	Remarks
Gan et al. (2011) Canada	Cohort study 418 826 adults 45–85 years old free of CVD at study start, living in Vancouver Exposure period: 1994–1998	LUR for zip code address for black carbon, PM _{2.5} , NO ₂ , NO Exposure period: 1994–1998 Median exposure: 30.6 µg/m ³ IQR: 8.4 µg/m ³ .	Risk of hospitalization and death from CHD in follow-up period 1999–2002	Single-pollutant model: RR: 1.04 (95% CI: 1.01–1.08) for CHD mortality per IQR (8.4 µg/m ³) of NO ₂ Three-pollutant model after adjusting for black carbon and PM _{2.5} : RR 1.03 (95% CI: 0.99–1.07) of NO ₂	Best predictor for CHD mortality was black carbon (per IQR, RR: 1.06 (95% CI: 1.03–1.09)). No effect of PM _{2.5} . NO ₂ correlated with black carbon with 0.39; NO ₂ correlated with PM _{2.5} with 0.47.
Hart et al. (2011) United States	Cohort study 53 814 men from trucking industry, 42 years old at baseline 1985	Annual average of PM ₁₀ , SO ₂ , NO ₂ for 1985–2000, from a model using spatial smoothing and GIS-based covariates, PM _{2.5} levels only for 2000 Mean exposure: 26.7 SD: 13.3 µg /m ³ IQR: 15 µg/m ³ .	All-cause mortality, death from lung cancer, CVD, IHD, respiratory system disease, COPD	Single pollutant model per IQR (8 ppb) of NO ₂ increase in: All-cause mortality: 8.2% (95% CI: 4.5–12.1%) CVD mortality: 6.9% (95% CI: 0.6–13.6%) Respiratory deaths: 5.9% (95% CI: -7.4–21.1%) Lung cancer: 5.5% (95% CI: -3.4–15.3%) Multipollutant models per IQR of NO ₂ increase in: All-cause mortality: 7.4% (95% CI: 2.4–12.5 %) CVD mortality: 6.8% (95% CI: -1.4–15.7%) Respiratory deaths: 5.6% (95% CI: -12.0–26.6%)	All pollutants associated more or less significantly with outcome. Highest effect estimator per IQR shown for NO ₂ . Effects diminished in multipollutant models most for PM ₁₀ , least for NO ₂ . Smoking was assessed in a smaller parallel survey and weakened the estimates for other pollutants.

BME: Bayesian maximum entropy; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; HR: hazard ratio; IHD: ischaemic heart disease; IQR: interquartile range; IDW: inverse distance weighting; LUR: land use regression; NO: nitric oxide; SD: standard deviation.

Table 8. Cohort studies from Europe on long-term mortality risk and NO₂ and PM without multipollutant models

Author (publication year) and location	Study design, population size and age, and study year	Pollutants (averaging time is for date range given)	Outcome measure	Effect estimates (95% CI)	Remarks
Heinrich et al. (2013) Germany	Cohort study 4752 women 55 years at study start 1985–1994.	One-year average of NO ₂ and PM ₁₀ (from TSP) until first examination at address at that time Proximity to traffic Mean NO ₂ exposure: 39 µg/m ³ Median: 41 µg /m ³ 75 th percentile: 45 µg/m ³ ; Range: 20–60 µg/m ³ .	Total mortality, cardiopulmonary mortality, lung cancer deaths until 2008	Per IQR of NO ₂ (16 µg /m ³) HR for total mortality: 1.18 (95% CI: 1.07–1.30) HR for cardiopulmonary mortality: 1.55 (95% CI: 1.30–1.84) HR for respiratory mortality: 1.13 (95% CI: 0.71–1.80) HR for lung cancer: 1.46 (95% CI: 0.92–2.33) Per 7 µg PM ₁₀ /m ³ HR for total mortality: 1.15 (95% CI: 1.04–1.27) HR for cardiopulmonary mortality: 1.39 (95% CI: 1.17–1.64) HR for respiratory mortality: 0.96 (95% CI: 0.60–1.53) HR for lung cancer mortality: 1.84 (95% CI: 1.23–2.74)	Proximity to traffic also associated with all-cause mortality. NO ₂ and PM ₁₀ were correlated (<i>r</i> = 0.5).
Beelen et al. (2008a) Netherlands	Cohort study 120 852 individuals aged 55–69 years in 1986	NO ₂ , BS, SO ₂ and traffic indices for 1976–1985 and 1987–1996; PM _{2.5} from PM ₁₀ 1992–1996 at address individually estimated. Mean NO ₂ exposure: 36.9 SD: 8.2 µg /m ³	Cardiopulmonary mortality, lung cancer deaths 1987–1996	Per 30 µg NO ₂ /m ³ RR for total mortality: 1.08 (95% CI: 1.00–1.16) RR for CVD mortality: 1.07 (95% CI: 0.94–1.21) RR for respiratory mortality: 1.37 (95% CI: 1.00–1.87) RR for lung cancer: 0.91 (95% CI: 0.72–1.15). Per 10 µg BS/m ³ RR for total mortality: 1.05 (95% CI: 1.00–1.11) RR for CVD mortality: 1.04 (95% CI: 0.95–1.13) RR for respiratory mortality: 1.22 (95% CI: 0.99–1.50) RR for lung cancer mortality: 1.03 (95% CI: 0.88–1.20)	Traffic density was also associated with total and CVD mortality with lower effect estimates. No significant association with PM _{2.5} or SO ₂ No individual risk factors No significant RR in case control study with individual risk factors for any pollutant

Author (publication year) and location	Study design, population size and age, and study year	Pollutants (averaging time is for date range given)	Outcome measure	Effect estimates (95% CI)	Remarks
Schikowski et al. (2007) Germany	Cohort study 4750 women, 55 years at study start 1985–1994	Five-year average of NO ₂ and PM ₁₀ (from TSP) until first examination at address at that time. Proximity to traffic Mean NO ₂ -exposure: 39 µg/m ³ Median: 46 µg/m ³ 75 th percentile: 49 µg/m ³ Max.: 55 µg /m ³	CVD mortality until 2002/2003	Per 16 µg NO ₂ /m ³ RR for CVD mortality: 1.72 (95% CI: 1.24–2.39) RR in sample with lung function measurements: 1.91 (95% CI: 1.22–2.98) RR for CVD mortality per 7 µg/m ³ PM ₁₀ : 1.64 (95% CI: 1.15–2.33) RR in sample with lung function measurements: 1.26 (95% CI: 0.75–2.14) All results independent of respiratory disease at baseline, which showed to be a higher mortality risk.	Publication with original analysis of cardiopulmonary mortality in Gehring et al. (2006) Correlation of pollutants not given
Naess et al. (2007) Norway	Cohort study , 143 842 adults in Oslo, 51–90 years at cut-off date: 1 Jan.1992	Dispersion model for NO ₂ , PM ₁₀ , PM _{2.5} as average 1992–1995 for 470 administrative areas Mean NO ₂ exposure: 39 µg/m ³ Range: 2–73 µg/m ³	All cause mortality, CVD mortality, mortality from lung cancer and from COPD 1992–1998.	All-cause mortality risk, all ages, increased over quartiles with most evidence above 42 µg NO ₂ /m ³ , above 19 µg PM ₁₀ /m ³ or above 14 µg PM _{2.5} /m ³ . Non-parametric analysis found a threshold for the younger age group above 40 µg/m ³ , but for the older age group there was an almost linear increase between 20 µg/m ³ and 60 µg/m ³ NO ₂ . Cause-specific mortality was associated with all pollutants, somewhat differently between age groups and sexes. Threshold seen for CVD death and lung cancer deaths, but not for COPD.	All pollutants correlated No information for smoking, but authors assume no impact, because of information from parallel studies Authors of the present section: The effects were particularly strong for COPD, which appeared to have linear effects, whereas cardiovascular causes and lung cancer seemed to have threshold effects.

Author (publication year) and location	Study design, population size and age, and study year	Pollutants (averaging time is for date range given)	Outcome measure	Effect estimates (95% CI)	Remarks
Filleul et al. (2005) France	Cohort study 14 284 adults from 24 areas in 7 cities 25–59 years old at study start 1974	Average (1974–1976) of SO ₂ , TSP, BS, NO ₂ and NO at monitors in study areas NO ₂ -average span in areas with monitors representative of residents: 12–32 µg/m ³ NO ₂ in the six areas excluded from analyses: 34–61 µg/m ³	Follow up of total natural mortality, deaths from cardiopulmonary diseases, and lung cancer until June 2001. Multivariate analysis was conducted for each pollutant, using the mean concentrations for the period 1974– 1976.	After excluding six areas with a high ratio of NO/NO ₂ (monitors next to high traffic): RR per 10 µg NO ₂ for nonaccidental mortality: 1.14 (95% CI: 1.03–1.25) RR for lung cancer 1.48 (95% CI: 1.05–2.06) RR for cardiopulmonary mortality: 1.27 (95% CI: 1.04–1.56) RR per 10 µg BS/m ³ for non- accidental mortality: 1.07 (95% CI: 1.03–1.10) RR for cardiopulmonary diseases: 1.05 (95% CI: 0.98–1.12)	No association of mortality with pollutants over all areas NO ₂ and TSP were correlated at 0.84; NO ₂ and BS were correlated at 0.85. TSP and BS showed weaker associations with total mortality and non-significant associations with the risk of cardiopulmonary mortality and lung cancer.

BS: black smoke; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NO: nitric oxide; SD: standard deviation; TSP: total suspended particles.

The following European studies are relevant to the evaluation.¹⁴

Recently, the results from a cohort of more than a million adults in Rome were published (Cesaroni et al., 2013). Long-term exposures to both NO₂ and PM_{2.5} were associated with increased risks of nonaccidental mortality. The strongest association was found for ischaemic heart diseases, but also mortality for cardiovascular diseases and lung cancer were significantly associated with both pollutants. Respiratory mortality was marginally associated with NO₂ and not associated with PM_{2.5}. The cohort was built on administrative data and lacked information on such behavioural risk factors as smoking (smoking was available on a subset of the cohort and no confounding from this factor was suggested in a sensitivity analysis). The models were therefore adjusted for pre-existing conditions that share lifestyle risks (diabetes, chronic obstructive pulmonary disease and hypertensive heart disease) and for individual and small-area socioeconomic position. The average exposure estimated for individual address for the follow-up (the mean follow-up duration was 8.3 years) was 43.6 µg/m³ (range: 13.0–75.2 µg/m³) for NO₂ and 23.0 µg/m³ (range: 7.2–32.1 µg/m³) for PM_{2.5}. The functional form of the association showed no evidence of deviation from linearity for non-accidental mortality, cardiovascular mortality, respiratory mortality and lung cancer, but it showed some deviation from linearity for the association between NO₂ and ischaemic heart disease mortality. In a two-pollutant model, the estimated effect of NO₂ on non-accidental mortality was independent of PM_{2.5}.

In a French study (Filleul et al., 2005) a comparison of mortality over a period of 25 years between 18 areas, including both NO₂ and black smoke, revealed positive and statistically significant effects of NO₂ – concentrations averaged between 12 µg/m³ and 32 µg/m³ over a period of 3 years for natural, cardiopulmonary and lung cancer mortality. The effects of black smoke were lower than those observed for NO₂. Six of the twenty-four areas with a NO₂ average from 36 µg/m³ to 61 µg/m³ were excluded from the analyses, as the monitors were not considered representative of the population's exposure (assessed with a high nitrogen oxide-to-NO₂ ratio, indicating localized traffic sources). In Germany, Heinrich et al. (2013) followed the vital status of women with baseline NO₂ and PM₁₀ exposure values for more than 18 years (SALIA study). Positive effects were found for all-cause and cardiopulmonary mortality in relation to NO₂ (median exposure: 41 µg/m³ in the year before baseline investigation, based on the annual average of the next monitoring station)) and for all-cause and cardiopulmonary mortality and for lung cancer mortality in relation to PM₁₀. The association between cardiopulmonary mortality and PM₁₀ was reduced in this extended follow-up period, during which PM₁₀ concentrations (but not NO₂ concentrations) were lower, compared with an earlier analysis, after 12 years (Gehring et al., 2006).

In contrast to the analyses of Gehring et al. (2006) and Heinrich et al. (2013), which investigated all-cause and cardiopulmonary mortality, the analyses of the SALIA-study data by Schikowski et al. (2007) investigated cardiovascular mortality risk in relation to NO₂ and PM₁₀, and a possible effect modification in women with impaired lung function or pre-existent respiratory diseases. The significantly elevated mortality risk from cardiovascular causes in relation to NO₂ (median exposure: 46 µg/m³) was not higher in the susceptible subgroup than in the whole sample. In an analysis of all inhabitants of Oslo, Norway, Naess et al. (2007) reported that the RR estimates for cardiovascular diseases, respiratory diseases and lung cancer were very similar for NO₂ and PM_{2.5} when evaluated across the quartiles of

¹⁴ The averaging times in this section are generally for the period of measurement (years) as set out in Tables 7 and 8.

the two pollutants. The Norwegian study also investigated the functional form of the association. The authors give separate results for the two age groups of 51–70 years and 71–90 years. In the younger age group, they observed a threshold for the effect on overall mortality of about $40 \mu\text{g NO}_2/\text{m}^3$ due to the results for cardiovascular and lung cancer mortality. Thresholds were also observed for $\text{PM}_{2.5}$ (about $14 \mu\text{g}/\text{m}^3$) and PM_{10} (about $19 \mu\text{g}/\text{m}^3$). In the older age group, the increase in overall mortality risk was linear in the interval $20\text{--}60 \mu\text{g NO}_2/\text{m}^3$. For chronic obstructive pulmonary disease, a linear effect was seen for both age groups. The large Dutch study by Beelen et al. (2008a) evaluated several pollutants, including NO_2 , $\text{PM}_{2.5}$ and black smoke. The effect sizes for natural, cardiovascular, and respiratory mortality were greater for NO_2 (population average: $36.9 \mu\text{g}/\text{m}^3$; SD: $8.2 \mu\text{g}/\text{m}^3$) than for $\text{PM}_{2.5}$ (population average: $28.3 \mu\text{g}/\text{m}^3$) and were similar to those for black smoke. The RRs per $30 \mu\text{g NO}_2/\text{m}^3$ were 1.08 (95% CI: 1.00–1.16) for natural mortality, 1.07 (95% CI: 0.94–1.21) for cardiovascular mortality and 1.37 (95% CI: 1.00–1.87) for respiratory mortality; the RRs per $10 \mu\text{g PM}_{2.5}/\text{m}^3$ were 1.06 (95% CI: 0.97–1.16) for natural mortality, 1.04 (95% CI: 0.90–1.21) for cardiovascular mortality and 1.07 (95% CI: 0.75–1.52) for respiratory mortality. The spatial correlation between different pollutants was high.

For cardiopulmonary mortality, the large American Cancer Society cohort study found no or a marginally significant association with NO_2 (a 1% increase per $18.8 \mu\text{g NO}_2/\text{m}^3$ in 1980 (95% CI: 0–2%)) and a marginally increased risk of ischaemic heart disease mortality (a 2% increase (95% CI: 0–3%) at a median exposure of $49 \mu\text{g NO}_2/\text{m}^3$). The study compared mortality and pollution between populated regions and was not designed to investigate smaller scale variations in pollution (Krewski et al., 2009). By contrast, a cohort study in Toronto, using land use regression to predict NO_2 at the residential address and an interpolation method to predict $\text{PM}_{2.5}$, did find a large effect on natural and cardiovascular mortality for NO_2 , but not for $\text{PM}_{2.5}$ (Jerrett et al., 2009b). Therefore, the authors modelled NO_2 together with traffic proximity (and not with $\text{PM}_{2.5}$), and the effects for NO_2 were slightly weakened, but still significant (from 1.40 (95% CI: 1.05–1.86) to 1.39 (95% CI: 1.05–1.85) per interquartile range of $7.6 \mu\text{g NO}_2/\text{m}^3$). The median of individually assessed NO_2 exposure was $43.05 \mu\text{g NO}_2/\text{m}^3$ (25th percentile: $39.1 \mu\text{g NO}_2/\text{m}^3$; 75th percentile: $38.46 \mu\text{g NO}_2/\text{m}^3$).

A new analysis of the California data from American Cancer Society Cancer Prevention Study II (Jerrett et al., 2011) used several different methods to model exposures to air pollution with high spatial resolution. It found, in a cohort of more than 76 000 adults with 20 432 deaths in the follow up period from 1982 to 2000, consistent associations of $\text{PM}_{2.5}$ with mortality from cardiovascular causes, comparable with the findings from the national American Cancer Society Cancer Prevention Study II. However, the strongest associations were found for NO_2 . Individual exposure data were derived from a land use regression model of NO_2 that predicted local variations in the exposure of participants in the years 1988–2002 (mean of individual level exposure 12.3 ppb or $23.1 \mu\text{g}/\text{m}^3$). The authors stated that NO_2 is generally thought to represent traffic sources and concluded that combustion-source air pollution was associated with premature death. The analyses are published as a report for the California Environmental Protection Agency Air Resources Board and are not (yet) published in a peer reviewed journal. The report does not give effect estimates with confidence intervals for the two-pollutant models.

Only a few of the studies reviewed conducted a formal multipollutant analysis designed to differentiate the specific effects of the pollutants. The large registry cohort study in Rome

found associations of NO₂ with non-accidental mortality, independent of PM_{2.5} and also independent of traffic density or distance to the next main road (Cesaroni et al., 2013). The analysis of the above-mentioned California data of the American Cancer Society Cancer Prevention Study II observed that, in two-pollutant models of NO₂ with PM_{2.5}, both pollutants were associated with significantly elevated effects on mortality from cardiovascular disease and ischaemic heart disease. NO₂ was also independently associated with an elevated risk for premature death from all causes and lung cancer (Jerrett et al., 2011), but the report did not provide the adjusted quantitative effect estimates.

Hart et al. (2011) examined the association of ambient residential exposure to PM₁₀, PM_{2.5}, NO₂, and SO₂ with mortality in 53 814 men in the United States trucking industry. One of the unique features of this study was the ability to model the mortality effects of exposures to multiple pollutants. In the multipollutant models, adverse effects were predominantly seen with exposures to NO₂ and SO₂, and they were reduced for PM₁₀ and PM_{2.5}. A weakness of the study was that there was no information on other risk factors for mortality, such as cigarette smoking. A subsample with information on smoking showed some correlation with pollution, and a recalculation, adjusting for smoking on that basis, suggested that the hazard ratio would be reduced in size but still remain – that is, it did not affect their qualitative conclusions. Similar findings are available from a Canadian cohort study (Gan et al., 2011), where the effects on mortality were stronger for black carbon and NO₂ than for other pollutants; the study used a multipollutant model (with NO₂, PM_{2.5}, and black carbon in the same model) that attenuated the NO₂ effect, but did not reduce it to null (RR =1.03, 95% CI: 0.99–1.07). It should be emphasized that the effect estimates for black carbon were robust against adjustment for NO₂, whereas the effect estimate for NO₂ was reduced to non-significance after adjustment for black carbon.

Overall, the findings suggest that traffic and other sources of fossil fuel combustion are important pollution sources that result in greater overall lung cancer, cardiovascular disease and respiratory disease mortality in the cohorts. In contrast to the cardiovascular mortality risk found to be associated with long-term exposure to NO₂ in the above studies, such an association was not found consistently in studies on the incidence or prevalence of cardiovascular disease. Only seven studies with cross-sectional, case-control or cohort designs investigated the relationship of these outcomes with NO₂ and particles in parallel. Five of those did not find any association or just a small insignificantly higher risk; two recent publications found an increased risk for ischaemic heart disease and for heart failure, but not for other cardiovascular diagnoses (Beckerman et al., 2012; Atkinson et al., 2013).

In summary, the European cohort studies provide evidence that the NO₂ effects on natural and cause-specific mortality are similar to, if not larger than, those estimated for PM. The recent registry cohort study from Italy (Cesaroni et al., 2013) and the American (Jerrett et al., 2011; Hart et al., 2011) and Canadian (Gan et al., 2011) studies have attempted multipollutant models, and they provide support for an effect of NO₂ independent from particle mass metrics. In three of these mortality studies with multipollutant models, the major fraction of the populations studied was exposed to NO₂ levels lower than 40 µg/m³; in one of them, nearly all participants were exposed to levels lower than 40 µg/m³ (Jerrett et al., 2011). Four of the six European analyses were centred around 40 µg NO₂/m³. In the French study, areas with (possibly non-representative) monitor averages above 32 µg NO₂/m³ were excluded. The study by Naess et al. (2007) looked at non-linear exposure–response functions and found a possible threshold around 40 µg/m³ for NO₂ and also a threshold for particles in the age group of 51–70-year-old people, especially for cardiovascular mortality. In contrast, they

found no thresholds in the age group of 71–90-year-old people for all cause and cardiovascular mortality and none for chronic obstructive pulmonary disease mortality in either age group. The Italian study found some evidence for non-linearity in the association between NO₂ and ischaemic heart mortality, but not for cardiovascular or non-accidental mortality. All other investigators applied linear exposure–response functions.

As the long-term mortality studies have all included populations exposed in part to annual average NO₂ concentrations of well below the current WHO air quality guidelines of 40 µg/m³, or even been conducted over a range almost entirely below the air quality guidelines, it would be wise to consider whether the guideline should be lowered at the next revision of the guidelines.

2.2 Sub-chronic and chronic toxicological studies

Animal studies

Since the 2005 global update of the WHO air quality guidelines, the toxicological evidence up to about 2007 has been described in several reports (EPA, 2008b; CARB, 2007; COMEAP, 2009b; WHO Regional Office for Europe, 2010). Table 9 summarizes the lowest effect concentrations at the lower end of the dose range, as highlighted in the conclusions sections of the various reports. Such studies as Mercer et al. (1995), highlighted by the EPA, that included spikes of higher concentrations have been excluded. It can be seen that there are now four studies showing effects below 0.34 ppm, including older studies not previously quoted by WHO, marked with an asterisk. Tabacova, Nikiforov & Balabaeva (1985) did not describe maternal toxicity,^{*15} so it cannot be determined whether the neurobehavioural posture and gait changes are a direct toxic effect of NO₂ on the offspring or an indirect effect, via toxicity to the mother. The study has not been replicated by other studies in this dose range, although similar effects have been found at much higher doses. The effects in the studies by Zhu et al. (2012) (reviewed in more detail below) and Takano et al. (2004)* are on risk factors for ischaemia and atherosclerosis, rather than actual occurrence of ischaemia and atherosclerosis themselves. Also, the change in endothelin-1 (Zhu et al., 2012) was in an unexpected direction, a direction that has not yet been replicated in another study. These three studies should not be dismissed, but there is an element of uncertainty in using them to describe a firm lowest effect concentration.

The publications by Sherwin & Richters (1995a,b)*, on the other hand, refer to a large study and to an effect that has regularly been shown at doses not far above 0.25 ppm. Tables in these three reports (CARB, 2007; COMEAP, 2009b; EPA, 2008b) describe no effect levels for various end-points in the range 0.04–0.5 ppm. No effect levels for morphological changes in the lung have been defined at 0.04 ppm for periods of 9 months or more (Kubota et al., 1987; Ichinose, Fujii & Sagai, 1991), but these studies were in rats, not mice, so whether weanling mice show effects below 0.25 ppm is unknown. It should be noted that these are research studies that examine selected end-points of interest rather than regulatory toxicology studies that examine a full range of end-points in one study or a package of linked studies. A *no effect level* for one end-point in a research study does not rule out effect levels for other end-points at similar concentrations.

It is not always clear from the epidemiology whether an effect apparently linked to long-term exposure is the result of a long-term process, or a cumulative reflection of the short-term

¹⁵ * This indicates older studies not referenced in earlier guidelines.

effects. In this respect, it is of interest that the studies by Sherwin & Richters (1995a) and Hyde et al. (1978) showed effects developing months to years after exposure ceased.

Two new sub-chronic animal studies on NO₂ alone have been identified from 2008 or later. Zhu et al. (2012) exposed healthy rats to 0.133 ppm and 2.66 ppm for 6 hours per day for 1 and 3 months. At 2.66 ppm, for 1 month and 3 months, there were increases in whole and relative blood viscosity, and red blood cell rigidity that were more marked at 3 months. The red blood cell aggregation and electrophoresis index were increased at 3 months. Effects at 0.133 ppm were not reported. In the brain cortex, protein expression of the endothelial function and inflammatory markers, eNOS, iNOS, COX-2 and ICAM-1 were increased at 2.66 ppm, but not 0.133 ppm, for 1 month. Endothelin-1, which triggers vasoconstriction, was reduced in a dose-related fashion, a result that was unexpected, as it was the reverse of what happened in 1-week experiments. The authors argue that, taking their short-term and long-term results together, NO₂ is an inducer and promoter of stroke.

Brandsma et al. (2008) found increased eosinophils in lung tissue, increased goblet cells, an increase in the cytokine IL-6 and a decrease in the anti-inflammatory cytokine IL-10 at 20 ppm of NO₂ for 1 month in mice. There were no signs of emphysema, but the study duration was short. A mixture study by Mauderly et al. (2011) suggested that it was possible that the reduction in TNF- α in bronchoalveolar lavage in rats by a simulated downwind coal combustion mixture containing 0.04–0.31 ppm NO₂, with or without sulfate particles, was due to the NO₂, but also noted that the study was not designed to identify causal pollutants.

Another mixture study, this time of inhalation of diesel exhaust from United States 2007-regulation compliant heavy duty engines, has recently been published (McDonald et al., 2012). This is a formal sub-chronic inhalation toxicology study in Wistar Han rats and C57BL/6 mice, with testing for a wide range of standard toxicological outcomes and three dose levels. The 2007 compliant engine has a particle trap that has reduced particle levels substantially and increased levels of NO₂. Here, NO₂ was used to standardize the dilution of diesel exhaust to give exposure levels of 0.11 ppm, 0.95 ppm and 3.6 ppm NO₂ in rats (16 hours a day; 5 days a week) for 13 weeks. The dilutions led to doses of 0.1 ppm, 0.8 ppm and 4.3 ppm NO₂ in mice. The rats showed statistically significant concentration-related changes in indicators that correlated with oxidative stress, mild inflammation, mild changes in lung function and mild lung pathology (increased epithelial cells at the terminal bronchioles and alveolar duct) at an exposure indicated by 3.6 ppm NO₂. At 0.95 ppm, similar effects were seen as part of the concentration-related trend but, apart from the indicators correlated with oxidative stress, were not statistically significant at that exposure level or even much changed from the low exposure in many cases. Lung pathology was absent, other than at the highest exposure. Apart from indicators correlated with oxidative stress, 0.1 ppm was a no effect level. Mice showed weaker effects (only minor inflammation at 4.3 ppm). None of the observed biological responses led to clinically observable morbidity at this time point in rats or mice. Based on comparisons with other studies, the authors considered that it was plausible that these effects were driven by NO₂, but acknowledged that this could not be conclusive, given the presence of other constituents. A further part of the same study (Conklin & Kong, 2012) found little effect on plasma markers of cardiovascular disease in young adult rats and mice, apart from transient effects on total cholesterol and HDL cholesterol.

Table 9 Lowest effect concentrations highlighted by WHO, EPA and CARB at low end of dose range ^a

Concentration	Duration	Species	Effect	Reference	Highlighted by	Comment
<i>0.04 ppm</i>	<i>9 months, continuous</i>	<i>Rats</i>	<i>Increased lipid peroxidation, measured by ethane exhalation</i>	<i>Sagai, Ichinose & Kubota (1984)</i>	<i>WHO (2006)</i>	<i>Could be adverse but can be reversible. Also quoted WHO (2010).</i>
0.05 ppm	6 hours a day, 7 days a week through gestation	Rats	Neurobehavioural postural and gait changes	Tabacova, Nikiforov & Balabaeva (1985)*	CARB (2007)	No description given of maternal toxicity. Dose-dependent effect. Did not persist beyond postnatal day 21.
0.13 ppm	6 hours a day for 1 month	Rats	Drop in endothelin-1 expression in cortex (unexpected direction)	Zhu et al. (2012)	This review	Dose-related. Other markers (eNOS, iNOS, COX-2 and ICAM-1) unaffected.
0.16 ppm	32 weeks, continuous	Rats (obese, non-obese)	Increased blood triglycerides, decreased HDL/ cholesterol ratio in obese rats	Takano et al. (2004)*	CARB (2007)	HDL also decreased in both obese and non-obese rats. Lowest dose tested: 0.16 ppm. Seen also at 0.8 ppm, but not at higher doses.
0.25 ppm	6 hours a day, 5 days a week, for 6 weeks, then air up to 32 weeks	Weanling mice	Potentially permanent lung changes (type II cell hyperplasia, increased elastin/alveolar wall ratio)	Sherwin & Richters (1995a,b)*	CARB (2007)	Type II cell hyperplasia delayed effect seen at 32 weeks. Increased elastin apparent at 6 weeks. Large study.
<i>0.34 ppm</i>	<i>6 hours a day, 5 days a week, for 6 weeks</i>	<i>Mice</i>	<i>Type I alveolar epithelial cells changed to type II bronchiolar Clara cells</i>	<i>Sherwin & Richters (1982)</i>	<i>WHO (2006)</i>	<i>WHO (2006) quotes review reports for this effect, as does WHO (2010) but cross-reference to the EPA and CARB reports suggests the Sherwin & Richters study.</i>
0.5 ppm	12 weeks, continuous	Weanling Brown Norway rats	Suppression of number and activity of alveolar macrophages	Kumae & Arakawa (2006)*	EPA (2008b)	
<i>0.5 ppm</i>	<i>24 hours a day for 6 months</i>	<i>Mice</i>	<i>Increased mortality from infection</i>	<i>Ehrlich & Henry (1968)</i>	<i>WHO (2006)</i>	<i>Also quoted (WHO, 2010).</i>
0.5 ppm	WHO (2010) states that “exposures to low levels of NO ₂ for weeks to months caused a variety of effects” rather than highlighting specific studies in their conclusions, but it does quote a number of studies with effects at 0.5 ppm in their detailed text.					
<i>0.64 ppm NO₂ (+ 0.25 ppm NO)</i>	<i>5.5 years</i>	<i>Dogs</i>	<i>Human type emphysema. Lung function continued to deteriorate after 2.5 years in clean air.</i>	<i>Hyde et al. (1978)</i>	<i>WHO (2006)</i>	<i>Thought due to NO₂ as less effect in co-exposure with higher NO. Also quoted WHO (2010).</i>

HDL: high-density lipoprotein.

^a For example, highlighted in the report summary and conclusions.

Note. Rows in italics present studies highlighted previously in other WHO reports.

Genotoxicity in vitro and in vivo, in animals and humans

Koehler et al. (2011) found weak evidence of DNA fragmentation and increased micronuclei (only after 3 hours) in human nasal epithelial cells at 0.1 ppm NO₂.¹⁶ This is the first in vitro genotoxicity test in human cells and shows effects at a lower concentration than previously (For context, in vivo mutagenicity tests give both positive and negative results (CARB, 2007; EPA, 2008b)). The Health Effects Institute (HEI, 2012) reported a micronucleus assay, employing flow cytometry performed in mice and rats; they used blood samples from the 3 month bioassay by McDonald et al. (2012), utilizing NO₂ within a modern diesel engine emission mixture, as discussed above. While there were some scattered significant findings, these did not form a coherent picture, and it was concluded that the results were negative in both rats and mice. Further studies will be done at longer exposure durations. Another analysis from this bioassay (Hallberg et al., 2012) found no effects of the mixture containing NO₂ on strand breaks in lung tissue, assessed with the comet assay, or on 8-hydroxy-2'-deoxyguanosine DNA adducts in the serum of rats or mice.

Another epidemiology study found increased urinary 8-hydroxy-2'-deoxyguanosine (a marker of oxidative DNA damage) in the elderly, with an increased 2- or 3-week moving average for NO₂ (daily average for NO₂: 17.8 ppb). This was not found for primary traffic pollutants (carbon monoxide, black carbon and elemental carbon), but was found for PM_{2.5}, sulfate and ozone (Ren et al., 2011). A further study found a borderline association between indoor NO₂ levels (13–18 µg/m³, averaging time not given) and micronuclei in blood cells of mothers and neonates (Pedersen et al., 2009).

Mechanistic epidemiology studies

In other mechanistic epidemiology studies, NO₂ was associated with elevated blood pressure, total cholesterol, fasting glucose, glycosylated haemoglobin and IL-6 in a cross-sectional study, but this was not maintained after adjustment for other pollutants (Chuang et al., 2011). NO₂ exposure during pregnancy increased CD-8⁺ T cells in cord blood. Whether these produced IL-4 was not described – this is of interest, as this type of T cell is higher in atopic asthmatics. In contrast, PM₁₀ reduced regulatory T cells (linked to predisposition towards allergy and asthma) (Baiz et al., 2011). Papers on gene-environment interactions between NO₂ and enzymes involved in reducing oxidative stress revealed some interactions, but study limitations (small subject numbers, measurement error, absence of replication) prevented definitive conclusions on the nature of these (Minelli et al., 2011).

Four further studies that reported interactions have been published since. Carlsten et al. (2011b), a small study in a high-risk cohort, showed the GSTP1 Ile105Val polymorphism conferring a weak trend to an expected increased risk of NO₂ associated asthma. Adding to the mixed picture on this polymorphism are earlier studies (Castro-Giner et al. (2009)

¹⁶ The evidence is clearest for the olive tail moment in the Comet assay, but less clear for % DNA in the tail or tail length.

found the interaction not significant; and Melén et al. (2008) found an interaction with allergic sensitization). Tung, Tsai & Lee (2011) found that NO₂ exacerbated the increased risk of polymorphisms increasing microsomal epoxide hydrolase activity on lifetime and early-onset asthma, but the biological hypothesis for this is via production of polycyclic aromatic hydrocarbon-derived quinones, rather than a NO₂ mechanism. Ungvári et al. (2012) studied polymorphisms in the Nrf2 gene (which coordinates the oxidative stress response) and found an interaction between a NO₂ and infection-induced asthma association and a polymorphism with an unknown function (not previously studied). Wenten et al. (2009) showed that the combined CAT–MPO genotype, predicted to protect most against oxidative stress, reduced the risk of respiratory-illness school absence linked to NO₂; this has not previously been studied.

This potentially important area of the literature may not be sufficiently mature as yet for firm conclusions. It should be noted that these studies did not control for exposure to PM (or, indeed, exposure to ozone), so it is unclear that these indicate susceptibility to NO₂ (per se) or to air pollution (in general), as indicated by NO₂.

3. Discussion

We are aware of the possibility that NO₂ has no direct effect itself but is, instead, only acting as a marker for primary particles, such as ultrafine particles, and such constituents as metals, polycyclic aromatic hydrocarbons or other organic matter carried on these particles to particular locations in the lung.¹⁷ NO₂ could also act as a marker for such gases as carbon monoxide or nitric oxide near roads or, as it is a secondary as well as primary pollutant, for regional pollutants such as ozone. Whether this is the case or whether NO₂ has a direct effect is a crucially important policy question. The implementation of filter traps in diesel vehicles to meet the Euro 5 emission standards and lowering sulfur in fuel, coupled with the fact that NO₂ levels are not being reduced in real-life driving conditions, may have led to important increases in the NO₂/ultrafine particle, NO₂/black carbon and NO₂/elemental carbon plus organic carbon ratios. For example, at a London roadside site, the ratio of nitrogen oxides as NO₂ (µg/m³) to particle number (N/cm³) changed more than twofold over 2 years (Jones et al., 2012). Comparison of data from the recent ESCAPE project, which covered the years 2008–2010 (Eeftens et al., 2012b; Cyrus et al., 2012), with the older TRAPCA project, which covered the year 1999 (Hoek et al., 2002a; Lewné et al., 2004),¹⁸ suggests that the traffic–urban background contrast for NO₂ has increased more over time than for PM_{2.5} absorbance (by about 10%). The rural–urban background contrasts showed a change of less than 10%. The changes in ratios are likely to be specific to location, site type and time period and would be better defined if there were more widespread and robust measurements of the relevant PM metrics over time.

¹⁷ It may even be acting as a marker for nitrogen oxides, which are highest near roads before the proportion of NO₂ is increased with distance as nitric oxide is oxidized to NO₂. However, nitric oxide is generally regarded as less toxic than NO₂.

¹⁸ The data are reported in: Table 5 of Hoek et al. 2002; Table 3 of Eeftens (2012); Table 4 in Lewne et al. (2004) and Table 4 in Cyrus (2012).

Given the change in these ratios, now and in the future, and between and within cities, there are clearly policies and behaviours that are changing NO₂ independently of other traffic pollution constituents. Unfortunately, there are no means in observational studies to fully test the hypothesis of a direct effect of NO₂. Adjustment of NO₂ associations for PM₁₀ or PM_{2.5} may not be sufficient, as there is often a closer correlation between NO₂ and traffic pollutants, such as primary PM and its constituents. Correlations with regional pollutants, such as ozone and secondary particles, are usually not as close.

Although the present document does not examine this point in detail, there are several key studies that show effects of NO₂ independent of ozone – for example, McConnell et al. (2003) and the review of multicity time-series study multipollutant models by Anderson et al. (2007).

Integration of the epidemiological evidence with chamber studies and toxicological evidence is, therefore, of considerable importance in judging whether there is an effect of NO₂ per se.

The discussions below relate mainly to respiratory effects, with a separate paragraph on cardiovascular effects. Effects on the environment are not covered, but are also important (Sutton et al., 2011).

Short-term exposure

In comparing the epidemiological and the toxicological and chamber study evidence for the concentrations at which effects occur, it is important to realize that, in the epidemiological studies, the daily variability at the background sites also reflects the daily variability at hot spots, so that the actual concentrations inducing health effects may be higher than those measured at the background site. Kerbside concentrations can be regularly in the range 380–560 µg/m³ (200–300 ppb) (1-hour average) at some polluted sites (London Air, 2013), and a wider range of sites often exceed the 1-hour limit value of 200 µg/m³ (EEA, 2012). This is within (or approaching) the range of concentrations that result in small effects in the chamber studies (380–1160 µg/m³; 200–600 ppb). Of course, it depends how long people are in those locations but, in addition to such activities as queuing at bus stops, in-vehicle exposure can be similar to the outdoor concentrations in heavy traffic (Chan & Chung, 2003), and car journey durations in congested cities can be considerable. Personal exposures to NO₂ reflect the sum of the microenvironment concentrations that an individual moves through over a determined time interval and are, therefore, strongly influenced by high concentration environments.

Concern has been expressed in some studies that ambient concentrations of NO₂ are not correlated with personal exposures to NO₂ and are, actually, better correlated with personal exposure to PM_{2.5} (e.g. Sarnat et al., 2001). However, a recent systematic review addressed the issue of the relationship between personal and ambient NO₂ exposures, identifying significant correlations between these two exposures estimates, though the strength of the association varied across studies (Meng et al., 2012). Studies not quoted

by Meng et al. (2012) also varied, both finding (Rijnders et al., 2001) and not finding (Bellander, Wichmann & Lind, 2012) significant correlations.

It is difficult to extrapolate quantitatively from animal toxicological studies. Modelling (with many assumptions) suggests about a tenfold higher local NO₂ concentration in the bronchi of humans than in those of rats, at the same concentration in the air that is being inhaled, and vice versa (much lower) in the alveoli (Tsujino, Kawakami & Kaneko, 2005). Several of the respiratory effects in animals occur in the bronchi, and it is plausible that some of the epidemiological results in human beings (such as asthma admissions) are primarily the result of effects on the bronchi. There may, therefore, be some evidence that supports application of the tenfold safety factors used in traditional toxicology for extrapolation from animals (strictly rats) to human beings. This, together with the distribution of personal exposures and the wide range of susceptibility in the human population, suggests that the epidemiological findings are not necessarily incompatible with the toxicological evidence on NO₂ itself. There are too few studies that examine NO₂ and particles from defined sources in the same experimental system, to directly compare the toxicological importance of these two pollutants, and their relative toxicological importance may vary by end-point.

The apparent mismatch between the time-series evidence and the lack of apparent responses in the chamber studies at background concentrations may be a consequence of only a small proportion of the population responding at particular times, an effect that could be picked up only in the much larger samples used in time-series studies. Specifically, more sensitive groups, such as severe asthmatics, are not studied in chamber studies because of the risks involved. Thus, the lack of robust effects and/or the lack of evidence at lower doses in chamber studies is insufficient to rule out the reported associations with NO₂ in the time-series studies found at the concentrations present in the wider environment. Considering the presence of more sensitive subgroups in the population together with the higher concentrations at microenvironments (such as the kerbsides described above) could explain some of the apparent mismatch, a point also made by Frampton & Greaves (2009).

While the preceding discussion supports the causality of the short-term respiratory effects, the issue is more uncertain for the short-term cardiovascular effects. Positive associations robust to adjustment for PM mass metrics are found in many time-series studies for cardiovascular mortality. The new evidence continues to suggest positive associations between NO₂ and cardiovascular hospital admissions, but findings are mixed in terms of robustness of the associations after adjustment for co-pollutants. It is therefore difficult to comment further on the nature of the relationship between NO₂ and cardiovascular hospital admissions. The results of panel studies on markers of cardiovascular risk (discussed in the toxicology section) found some interesting results in some cases, but no effects in others. Of the few chamber studies available, most did not find effects on cardiovascular end-points. The few short-term animal studies available did find effects on markers of systemic oxidative stress, inflammation and endothelial dysfunction at above ambient concentrations, but without a defined no-effect level. One study found that plasma from volunteers exposed to NO₂ at 0.5 ppm had an effect on

coronary epithelial cells in vitro. Although slightly longer term (3 months), the study of modern diesel emissions, more highly dominated by NO₂, did not find evidence of cardiovascular effects in healthy young animals. There are theoretical mechanisms by which NO₂ inhalation could cause increased nitrative stress in the diseased heart. The overall picture is mainly one of an absence of a sufficient volume of evidence to resolve the mixed results found in the studies available, so it adds uncertainty, rather than challenging the causality of the epidemiological associations.

The current short-term guideline has the advantage of being set on the basis of chamber studies that use NO₂ itself. However, there is now a large body of time-series and panel evidence that, in contrast to other pollutants, has not been used so far in determining the level of a short-term guideline. It is recommended that this evidence be included in future considerations of a short-term guideline for NO₂.

Long-term exposure

Another challenging issue is whether the effects of long-term exposure are due to NO₂ per se.

Human chamber studies are not suitable for investigating long-term exposures. While animal toxicological studies do provide evidence of long-term effects, the degree to which this applies at ambient concentrations is less clear. In studies that compare long- and short-term exposures, the effects of long-term exposures occur at lower concentrations (0.25 ppm for clear adverse effects and some possible effects below this (Table 9)). However, while this concentration can be found at kerbsides, it is less likely that people are exposed to these concentrations several hours a day long-term (the long-term toxicological studies were often not based on exposure for 24 hours a day) than it is for people to be exposed for the shorter durations needed for the short-term effects. The toxicological evidence now includes a few studies that show cardiovascular effects, but the evidence is too limited for firm conclusions. It is much harder to judge the robustness to adjustment in the long-term epidemiological studies than it is in the short-term studies, because the spatial correlations between NO₂ and other pollutants are often high. However, there are a few studies that do suggest effects independent of particle mass metrics (including studies on cardiovascular mortality). The existence of effects of short-term exposure provides some plausibility for the effects of long-term exposure – particularly, for respiratory effects.

In summary, there is also some support, to a lesser degree than for the short-term, for a long-term effect of NO₂ per se. Again, NO₂ may also be capturing the effects of other traffic-related pollutants.

The current long-term guideline developed historically from one based on indoor studies. Now, there are enough outdoor air pollution studies (those described here plus pre-2004 studies) on respiratory effects and on all-cause mortality to consider using them to help set a new long-term guideline, with appropriate caveats about uncertainties. These studies included exposures to concentrations above and below, or all below, the current guideline

and, where studied, linear relationships without a threshold have been found for at least some outcomes. This suggests that consideration should be given to lowering the guideline.

How to reflect these uncertainties in regulations is a matter beyond the scope of WHO, but consideration could be given to flagging the guideline to emphasize uncertainty.

Research gaps will be highlighted later in answers to Question C9, but it should be emphasized – particularly for NO₂ – where much of the important chamber and toxicological evidence comes from 20–30 years ago. Information on mechanisms is crucial and needs to take advantage of the full range of modern experimental techniques, including systems biology, to capture interacting causal pathways.

Question C3

Based on existing health evidence, what would be the most relevant exposure period for a short-term limit value for NO₂?

Answer

The most relevant exposure period based on existing evidence is 1 hour because 1-hour peak exposures in chamber studies have been shown to produce acute respiratory health effects. Toxicological studies also support the plausibility of responses to peak concentrations. Time-series and panel studies have examined associations, using both 24-hour average and 1-hour average NO₂ concentrations with similar results. Evidence from these studies would support the development of a 24-hour WHO guideline or a 1-hour guideline but, as there is chamber study and toxicological evidence on, or close to, a 1-hour basis and much less evidence on a 24-hour basis, a 1-hour exposure period is preferred. In urban areas, 1-hour peak concentrations and 24-hour averages were so highly correlated that it should be possible for a 1-hour peak guideline to be derived from studies using 24-hour average NO₂, following expert analysis of how these metrics are related in Europe. There is, therefore, no need to develop a 24-hour limit value in addition to a 1-hour guideline based on epidemiological studies.

Rationale

1. Time-series studies

The majority of time-series studies have examined associations using 24-hour averages of NO₂ concentrations, with fewer using maximum 1-hour averages. The studies have reported associations that suggest adverse mortality and morbidity effects at concentrations below the current 1-hour WHO air quality guideline for NO₂. Consistent findings of positive associations with respiratory and asthma hospital admissions have been reported. These findings are in keeping with the outcomes investigated in chamber studies, which demonstrate direct effects of NO₂ over a few hours. Such evidence of direct effects in the chamber studies led to the development of the current short-term guideline. Given the close correlations that exist between 1-hour and 24-hour measures – for example, the range of correlation coefficients between the maximum daily 1- and 24-hour NO₂ concentrations across the 29 European cities in Samoli et al. (2006) was 0.80–0.94, with a median of 0.90 – a 1-hour guideline could be converted to a 24-hour one. Samoli et al. (2006) also reported that, in European cities providing both 1-hour and 24-hour average concentrations of NO₂, the ratio between the two measurements was 1.64. This could be used to scale a 24-hour average concentration–response function to a 1-hour-average concentration–response function that could then be used to set a time-series-based 1-hour guideline.

2. Panel studies

The panel studies of respiratory effects in asthmatic children have generally used 24-hour averages as the shortest averaging period. As with the time-series studies, this does not necessarily mean that 24-hour continuous exposure is required before effects are found.

3. Chamber studies

The chamber studies on human beings examined exposure intervals over periods of 30 minutes to 6 hours, with 1 hour being a common exposure period. Comparisons of durations within the same experiment were not widely done, and a comparison of the effect of different durations across experiments is difficult, given the weakness of the effect itself (clinically significant effects have only been reported at relatively high concentrations in mild disease – see the discussion for Question C2). There is a great need to know whether NO₂ per se has direct effects in severe and hyperreactive asthma. No such chamber studies have been conducted (and would be unlikely to be conducted), and thus the time period for severe asthmatics to respond is unknown. After review of the recent literature – albeit, in mild asthma, but with a range of nonspecific airway hyperresponsiveness – there appears little reason to alter the level or averaging time of the current 1-hour average limit value, from the chamber study perspective.

4. Toxicological studies

It is apparent from the previous three sections that the evidence depends on the averaging time (for the time-series and panel studies) or exposure period (for the chamber studies) chosen for study. For the time-series and panel studies, the averaging time chosen is driven by the monitoring data available, rather than any mechanistic considerations, and this leads the discussion to a comparison of 1-hour and 24-hour averaging times. The question, however, does not relate only to 1-hour and 24-hour average exposure periods. Do toxicological studies that have more flexibility in the exposure periods chosen for study indicate any other exposure period would be more appropriate?

a. Is there evidence on the time scale over which NO₂ or its reaction products reach potential targets for toxicological effects?

Enami, Hoffmann & Colussi (2009) suggest that the uptake of NO₂ gas across the air–liquid interface – via conversion into hydrogen and nitrate ions and nitrous acid – occurs within milliseconds. Absorption into bronchoalveolar lavage fluid via reaction with antioxidants in vitro was already apparent within 30 minutes at environmentally relevant concentrations (Kelly & Tetley, 1997). At 20 ppm, NO₂, containing the isotopic nitrogen-15 label, was present in perfused rat lung tissue (soluble and insoluble components) and in the perfusate, probably as nitrite, (analogous to the blood supply) after inhalation for an hour (shorter durations were not tested) (Postlethwait & Bidani, 1989). The NO₂ radical (derived from nitrite) had an estimated permeability coefficient of 5 cm per second across lipid membranes, suggesting lipid membranes are not a significant barrier to NO₂ transport (Signorelli et al., 2011).

b. What was the exposure period for the lowest effect concentrations in short-term toxicology studies described in Question C2?

An increase in mast cell numbers occurred in rat bronchi after 3 hours at 0.2 ppm NO₂ (Hayashi & Kohno (1985), quoted in CARB, 2007); altered behaviour of detoxification enzymes (measured by pentobarbital sleeping time) occurred in mouse livers after 3 hours at 0.25 ppm (Miller et al., 1980); biosynthesis of the carcinogen dimethylnitrosamine in dimethylamine-treated mice was detected after 30 minutes at 41.5 ppm or 2 hours at 0.1 ppm (Iqbal, Dahl & Epstein, 1981); and increased proliferation of bronchiolar tissue was found after 24 hours at 0.8 ppm (Barth et al., 1994) These were usually the shortest durations tested, so it is unknown whether shorter durations could have had the same effect.

c. Is there evidence that peak concentrations are particularly important?

Defining a guideline on the basis of a shorter exposure period has the effect of controlling peak concentrations more strongly. In toxicological studies, both concentration and time (and, hence, the total amount of chemical delivered) can contribute to the development of effects, but the relative importance of concentration and time may differ for chemicals with different mechanisms. For example, antioxidant defences may handle the same amount of NO₂ more easily if presented as a lower sustained exposure, where there is time for induction of antioxidant enzymes to occur, than if presented in a short peak that would overwhelm the antioxidant defences. Although their study was related to long-term exposure and high concentrations, Rombout et al. (1986) investigated the relative importance of peaks of NO₂ for morphological changes in the rat lung. The onset of effects on the bronchiolar epithelium occurred earlier and was more serious at 10.6 ppm intermittently (6 hours a day) for 4 weeks than at 2.7 ppm continuously for 28 days (exposures with the same product of concentration and time), so it was concluded that concentration played a more important role than duration. For the influx of macrophages, continuous exposure was more important than intermittent exposure. This was confirmed by Frampton et al. (1989), who found that macrophage activity was affected more in 4 of 9 human volunteers exposed to 0.6 ppm continuously for 3 hours than it was for a background of 0.05 ppm for 3 hours with three 15 minute peaks at 2 ppm (both 108 ppm-minutes).

Miller et al. (1987), however, compared the effect in mice of a continuous 0.2 ppm background exposure 5 days a week for 1 year, and with the same background exposure (but also with a 0.8 ppm spike for an hour twice a day) and found that mortality from infection and the effect on pulmonary function were greater in the presence of spikes. Peaks of 4.5 ppm for 1, 3.5 or 7 hours increased mortality when a *Streptococcus* challenge was given immediately afterwards; but when given 18 hours later, only the 3.5- and 7-hour duration peaks increased mortality in mice (Graham et al., 1987). This suggests recovery is more likely for the shorter durations. It is not necessarily the case that the importance of peaks compared with duration will be the same for different outcomes. It is also worth noting that many of the longer-term toxicological studies only involved exposures for 6 hours during the day for weeks or months, not 24 hours a day.

A short-term guideline, while set on the basis of short-term exposure studies, may nonetheless have a role in reducing the likelihood of longer-term effects, by controlling peaks. In summary, while the importance of peaks may vary for different outcomes, there is some evidence that peaks are important.

5. Discussion

There is relatively little research aimed directly at assessing the importance of duration of exposure, and many of the toxicological studies that address this are at high doses. Nonetheless, there is some indication that shorter durations may be more important than longer ones, at least for some end-points. There is no strong evidence to argue against using a 1-hour exposure as used in the current guideline.

The question assumes just one short-term limit value. There is an argument for having both a guideline set on the basis of chamber studies, where the toxic agent is known to be NO₂, and a further guideline set on the basis of the large body of time-series studies that show the effects at lower concentrations, but with more uncertainty as to the responsible indicator pollutant for health effects. This would make the WHO view on the different types of evidence more transparent. These could subsequently be pooled for regulations. Given the evidence that an hour is sufficient to cause effects, it is not clear what might be the added health benefit of adding a 24-hour average guideline for NO₂. This is not to say that the 24-hour average concentration time-series evidence cannot be used. As explained earlier, examination of the relationship between 24-hour and 1-hour average concentrations of NO₂ in Europe should enable conversion of concentration–response functions from 24 to 1 hour and/or indicate whether a 24-hour average guideline expressed in 1-hour average terms is tighter than the 1-hour average guideline based on chamber studies. The tighter guideline can then be used as the basis for the standard. Alternatively, the subset of time-series studies that use maximum 1-hour averages could be used to set the time-series-based guideline, although there are fewer studies to choose from.

Question C4

Based on currently available health evidence, what NO₂ metrics, health outcomes and concentration–response functions can be used for health impact assessment?

Answer

This answer assumes an application in a health impact assessment of NO₂ itself, given that impacts of other pollutants – notably PM mass – are also being quantified. The use of NO₂ as an indicator for a health impact assessment of local traffic measures is discussed in the rationale. The evidence base supports quantification of effects of short-term exposure, using the averaging time as in the relevant studies. The strongest evidence is for respiratory hospital admissions, with some support also for all-cause mortality – these are recommended outcomes for use in the core analysis. Cardiovascular hospital admissions can be included as a sensitivity analysis – the evidence is more uncertain than for respiratory admissions. It is recommended to derive concentration–response functions from time-series studies that have provided effect estimates for NO₂ adjusted for at least PM mass.

For a core health impact assessment of effects of long-term exposure to NO₂, the recommended health outcome is bronchitic symptoms in asthmatic children, with the coefficient adjusted for a PM metric based on the Southern California Children’s Health Study. A health impact assessment using asthma prevalence could also be performed. However, as only estimates from single-pollutant models are currently available for asthma prevalence, this health outcome should only be used in sensitivity analyses that compare results with those of health impact assessments for PM mass.

Cohort studies also show relationships between long-term exposure to NO₂ and mortality, but not all are sufficiently robust for use in a core health impact assessment. Therefore, the effect of long-term exposure to NO₂ on all-cause mortality is recommended for sensitivity analysis only. Concentration–response functions from cohort studies with effect estimates for NO₂ that were adjusted for at least PM mass should be used. In the same way, cardiovascular mortality could also be included in a sensitivity analysis, due to the uncertainty about a mechanistic understanding of cardiovascular effects.

Rationale

1. Context in which the concentration–response functions will be used in health impact assessment

It is important to emphasize that the appropriate concentration–response functions to choose will vary according to the context of the health impact assessment. Some of the factors to be taken into consideration (and the questions that relate to them) are set out below, particularly in terms of whether the concentration–response functions are being

used to assess effects of NO₂ itself or are being used as an indicator of a mixture associated with NO₂.

- a. Is the primary purpose of the health impact assessment to estimate the burden of current air pollution or to assess the health impacts of a change? In general, in a health impact assessment, use of an indicator pollutant is inappropriate for evaluating a change: but such an assessment has less uncertainty in estimating a burden, rather than a change, if based on epidemiological studies from a similar pollution environment – in terms of date and type of area. However, since policy is about change, burden calculations are used more in the context of *alerting people to the current problem* than for sophisticated future policy analysis. This is because *current air pollution* is more likely to have a correlation pattern between pollutants similar to that of the situations where the epidemiological associations were derived, whereas a change is more likely to lead to a different correlation pattern between pollutants. This would mean that indicator pollutants would no longer act as indicators in the same way.
- b. If the health impact assessment is about the impact of a change (involving a change in NO₂), what exactly is causing the pollution change and what does that imply for pollutants other than NO₂? For example, for local traffic measures, is it about reducing local traffic as a whole, or about reducing emissions of NO₂ specifically?
- c. What is the spatial scale of the health impact assessment? The role of NO₂ as an indicator may vary with spatial scale (close to roads; within a city; and between cities and regions).
- d. What other pollutants are included in the health impact assessment model? There are at least four possibilities available to address this; these possibilities can vary with both context and outcome, as outlined in the following questions and remarks:
 - i. modelling of effects of other pollutants, such as PM_{2.5}, with quantification of relationships with NO₂ intended to supplement this – that is, is there reasonable confidence in an effect of NO₂ itself being additional to other pollutants;
 - ii. *what if* scenarios (sensitivity analysis), where there is more confidence in the effect of the other pollutant(s) than in NO₂ – that is, “if the possible effect of NO₂ is true, what might the additional effect be;
 - iii. *what if* scenarios (sensitivity analysis), where it is unclear which pollutant is responsible – that is, if this pollutant were responsible, there could be an effect of *x*; if NO₂ were responsible, there could be an effect of *y*, so the effect is likely to lie in the range of *x* to *y*; and
 - iv. in circumstances where quantification of effects of, for example, PM_{2.5}, is too difficult (such as those for which measurements are unavailable), or where a traffic measure is not changing the composition of the emissions or the fleet (such as pedestrianization) – NO₂ is being used as an indicator.

Coefficients adjusted for other pollutants would be appropriate for (i) and (ii), whereas single-pollutant models would be appropriate for (iii) and (iv).

The main question for this section does not specify the context of the health impact assessment. As our main case, we have assumed that policy measures that may affect NO₂ independently are being assessed and that other pollutants are also being quantified (item d(i–iii) above). Other alternatives, which can also be important (item d(iv)), will be mentioned at various stages in the text below. A summary in Table 10 at the end of the section will help make the recommendations clear.

It is important that the full range of studies should be considered, not just those since 2004 that have been considered in detail in this review. While we have mentioned some earlier studies of which we are aware, we understand that meta-analyses of (or selection of a representative study from) the full range of studies will be performed by another project. We concentrate here on the appropriate outcomes and metrics and on studies or areas of evidence that could be used as sources of concentration–response functions. However, firm recommendations for specific concentration–response functions await further work by this separate project.

2. Effects of short-term exposure

Respiratory hospital admissions. The most consistent evidence comes from short-term epidemiological studies of respiratory morbidity, and this is supported by chamber-study and toxicological evidence (see Question C2) – this can be used in the central analysis (see item d(i) above). We recommend using respiratory hospital admissions for all ages. The averaging times from the relevant studies could be used in health impact assessments, as the majority of studies available used 24-hour average concentrations of NO₂. Whether or not to use coefficients adjusted for other pollutants also needs to be considered, and this may affect the choice of metric. Coefficients adjusted for at least PM mass should be considered. There are more adjusted coefficients available for 24-hour average NO₂ than for the 1-hour average. Coefficients could be selected either from a representative multicity study or a meta-analysis of all available studies. As well, an existing meta-analysis – for example, Anderson et al. (2007) – could be used, though this would not reflect more recent studies. If there is specific interest in a health impact assessment using maximum 1-hour average concentrations of NO₂, consideration could be given to converting the larger body of evidence on associations with 24-hour average NO₂ to a maximum 1-hour average concentration–response function (see Question C3). As explained earlier, examination of the relationship between 24-hour and maximum 1-hour average concentrations of NO₂ in Europe would be required to enable conversion of concentration–response functions from 24 hours to maximum 1 hour. Whether it is appropriate to convert an adjusted 24-hour coefficient (derived by meta-analysis or selected from a paper) to one for maximum 1-hour is unclear.

Cardiovascular admissions. The epidemiological associations for cardiovascular admissions are not generally robust to adjustment for co-pollutants; there are very few

chamber studies or toxicological studies on cardiovascular end-points available, and those that exist are contradictory (see Question C2). The evidence on PM and cardiovascular admissions is stronger. We therefore recommend that concentration–response functions for cardiovascular admissions are used *only* in sensitivity analysis as a *possible* effect additional to PM (that is, item d(ii) above) or when using NO₂ as an indicator (item d(iv) above).

The same points about metrics and adjusted coefficients, discussed above for respiratory hospital admissions, apply for cardiovascular admissions.

All-cause mortality. Given that respiratory hospital admissions are to be quantified in a central analysis, there is also some plausibility for an effect on respiratory mortality; and, indeed, consistent associations with respiratory mortality have been shown in many cases. Associations have also been shown for cardiovascular mortality but, as mentioned above, the issue of causality is more uncertain. However, since there can be issues about cross-diagnosis between respiratory and cardiovascular deaths and since baseline rates for all-cause mortality are widely available, we recommend use of concentration–response functions for all-cause mortality for all ages for the central analysis (item d(i) above), acknowledging a certain additional level of uncertainty compared with respiratory admissions.

For health impact assessments, the same points about metrics and adjusted coefficients as for respiratory hospital admissions above apply. If it is not possible to do a meta-analysis of the larger body of literature to derive a coefficient, estimates could be based on Samoli et al. (2006), which presents pooled results from 30 cities in Europe using maximum 1-hour average NO₂ concentrations with adjustments for PM₁₀ and black smoke. The NO₂ estimate adjusted for black smoke (a good indicator of primary combustion particles) would better reflect a possible NO₂ per se effect than would a coefficient adjusted for PM₁₀. If a meta-analysis is possible, multiple studies are available on adjusted coefficients for 24-hour average NO₂ concentrations, although thought would need to be given to which pollutant-adjusted coefficients to use. Use of a coefficient adjusted for PM is suggested. Multiple studies are also available on 24-hour average single-pollutant models (fewer studies are available for the maximum 1-hour average), for circumstances where this would be appropriate (for example, when other pollutants are not being quantified (item d(iv) above) or where the dangers of double counting are openly acknowledged (for example, item d(iii) above).

3. Effects of long-term exposure

As mentioned in part 1 of Question C4, we have assumed as our main case that policy measures that may affect NO₂ independently are being assessed and that other pollutants are also being quantified (item d(i–iii) in part 1 above). Quantifying the effects of NO₂ itself is particularly challenging. This will be addressed first. The importance of capturing the health impacts of traffic pollution, which might otherwise be missed, is discussed second – that is, scenarios as described in item d(iv) of part 1 of Question C4. Within

each of the following sections, respiratory effects are considered first when discussing the health outcomes – given the greater degree of mechanistic evidence supporting the effect.

3.1 NO₂ per se

When both PM metrics and NO₂ measures are used in health impact assessments, some of the effects attributed to each of them may overlap. So, estimates from two-pollutant models should be used to attempt to avoid this. Unfortunately, very few long-term studies provide estimates from two-pollutant models (see Question C2), often because NO₂ and PM were too closely correlated. In addition, papers may not perform two-pollutant models when one of the pollutants did not show a significant association.

Studies that examine NO₂ using exposures based on a few monitoring sites as a broad surrogate for personal exposure may have lower correlations with primary particle metrics. But this advantage may be offset by the exposure measure being less representative of individual personal exposure (measurement error) and, therefore, showing weaker effects in two-pollutant models, independent of a possible so-called true association. Correlations with PM mass metrics may be higher in such studies. This illustrates the point that the spatial scale of the study can influence the interpretation of the concentration–response function to be used in the health impact assessment.

Black carbon, elemental carbon or black smoke, and carbon monoxide, being alternative measures to capture traffic exhaust effects, share with NO₂ the aspect of traffic proximity and association with emissions from combustion. They are often more closely associated with NO₂ than with particulate mass. It is self-evident that the results of an impact assessment for those indicators should not be added with the results for NO₂, if single-pollutant models are being used.

The health outcomes associated most consistently with long-term exposure to NO₂ are mortality, respiratory symptoms or asthma, and lung function. Cardiovascular outcomes are more uncertain – not because there is a large body of evidence showing a lack of effects, but because there are relatively few studies and there is less support from mechanistic evidence. The degree to which these associations are a consequence of NO₂ per se was discussed in Question C2, and the points relevant to choices of concentration–response functions are highlighted below for each end-point.

Children’s respiratory symptoms and/or asthma symptoms. As discussed in Question C2, there are several cohort studies that show the effects of long-term exposure to NO₂ on the respiratory condition of children. Several of these effects were related to lung function, which is a difficult end-point to use in a cost–benefit analysis, as it does not necessarily correspond exactly with symptoms and is therefore hard to give a value in monetary terms (The end-point could be used in cost–effectiveness analysis). Nonetheless, the finding in some studies of an effect on lung function that is stable to adjustment for other pollutants provides some support for the studies that examine respiratory symptoms. Publications from the Southern California Children’s Health Study include a paper on bronchitic symptoms in asthmatic children; the paper used

multipollutant models for a variety of PM metrics, as well as NO₂ and ozone (McConnell et al., 2003). While the effects of NO₂ and organic carbon were difficult to separate, associations with NO₂ were found both across communities and across different years within communities, whereas associations with organic carbon were only robust in the latter case. An adjusted coefficient from this study could be used, although the end-point of bronchitic symptoms in asthmatics, as a result of year-to-year variations in annual average NO₂, is rather unusual, and there are an insufficient number of studies with adjusted coefficients to perform a meta-analysis. It is difficult to judge whether to use this coefficient for a central analysis. For the evidence currently available, it is the least uncertain of the possible concentration–response functions, as it has an adjusted coefficient and is for a respiratory outcome. Although it is only one study, it is supported in a general way by epidemiological long-term exposure studies that show effects on lung function. For now, before further studies are available, we suggest the use of the adjusted coefficient in a central analysis (item d(i)) above, with acknowledgement of the greater degree of uncertainty (see the summary in section 4 below), compared with other central analysis effects.

There are meta-analyses available for NO₂ and asthma incidence (Anderson, Favarato & Atkinson, 2013b) within communities (positive) and for NO₂ and asthma prevalence across communities (no associations) (Anderson, Favarato & Atkinson, 2013a). There are also several studies of NO₂ and asthma prevalence within communities (most positive) that would be suitable for a meta-analysis. Annual prevalence would be preferable for quantification, particularly as the asthma incidence meta-analysis was intended only for hazard assessment and, thus, did not control for the length of the follow-up period. As correlations were so close, multipollutant models were not available. Nonetheless, these studies could be used to provide coefficients for a sensitivity analysis that compares the possibilities of the effect being entirely due to black smoke, entirely due to NO₂, or (more likely) somewhere in between (item d(iii) above).

Mortality. There is now a good body of evidence on NO₂ and all-cause mortality in within-community cohort studies. Unfortunately, there is no recent meta-analysis, and only a few of the studies could apply two-pollutant models (see Question C2). A large cohort study investigating multipollutant models with NO₂ (Jerrett et al., 2011) did not yet provide exact estimates with confidence intervals for the two-pollutant model NO₂–PM_{2.5}. However, the recent large Rome Longitudinal Study (Cesaroni et al., 2013) provided effect estimates for NO₂-related natural mortality, while adjusting for PM_{2.5} in a two pollutant model. In addition, the Canadian study (Gan et al., 2011), which investigated the association of coronary heart disease mortality with the three pollutants PM_{2.5}, black carbon and NO₂ together, could (in theory) serve as a cautious approach in sensitivity analysis for calculating independent effects of NO₂ from particulate mass and from traffic soot. NO₂ had correlation coefficients with PM_{2.5} and black carbon of 0.47 and 0.39, respectively. It should be noted, however, that this study used a population free of cardiovascular disease at baseline, rather than the general population, so general population baseline rates would not apply. Results from more (including large) cohort studies with results on NO₂ in multipollutant models are expected in the near future, together with comprehensive meta-analyses. The additional uncertainty about other

supporting evidence for cardiovascular effects would need to be acknowledged. The best option would be to use an adjusted all-cause mortality estimate from the studies expected in sensitivity analysis (item d(ii) above), due to uncertainties about the causality of the cardiovascular component of all-cause mortality. Alternatively, a meta-analysis of single-pollutant models could be used in sensitivity analysis (d(iii)) to compare (but not add) the possible effects, if the relationship is due to NO₂, compared with it being due to PM.

3.2 Capturing the effects of traffic pollution and/or small-scale variations in pollution

NO₂, particularly primary NO₂ from traffic, shows a much larger spatial variation than does PM_{2.5}. With regard to health impact assessments, PM_{2.5} is not optimally suited to capture long-term effects from small-scale spatial pollution variations (Beelen et al., 2008a; Bemis, Torous & Dertinger, 2012). A health impact assessment that intends to estimate *the whole burden of air pollution* will miss these effects, if it relies only on PM_{2.5}. The additional burden of small-scale variations in pollution can be estimated by using NO₂, as it has been found to be associated with effects not always captured by using PM mass (Jerrett et al., 2009b), in studies where individual exposure to pollution was estimated with more spatially exact methods (such as land use regression models). Especially in Europe, NO₂ has therefore been used to investigate the effect from traffic pollution (Brunekreef, 2007; Cesaroni et al., 2013).

A health impact assessment intended to estimate *only the long-term health effects of traffic pollution* could rely on single-pollutant model concentration–response functions for NO₂, alternatively or as a sensitivity analysis to an evaluation of effects associated with PM mass. In that case, estimates from one-pollutant models could be used. The respective results can be compared, but not added. The caveat is that NO₂ might not be acting as a marker for traffic in the same way it did at the time of the study – for example, due to the use of particle traps increasing emissions of primary NO₂, (see Question C2).

Children’s respiratory symptoms and/or asthma symptoms. The McConnell et al. (2003) study (described in section 3.1, on NO₂ per se) is less obviously suitable for a concentration–response function that represents pollution varying on a fine spatial scale, such as traffic pollution, as the study is based on a combination of cross area comparisons and yearly variations. The yearly variation within community component (which may be driven more by local pollution sources) has, however, been used in health impact assessments of local pollution changes (Perez et al., 2009b; Perez et al., 2012; Brandt et al., 2012).

The meta-analyses available for NO₂ and asthma incidence (Anderson, Favarato & Atkinson, 2013b) within communities (positive) – or (better (see 3.1)) the studies of NO₂ and asthma prevalence within communities (most positive) that have the potential for meta-analysis – are suitable for quantifying the effect of traffic pollution or fine scale varying pollution, in general (that is, d(iv)), where other traffic pollutants are not quantified. To quantify the effect of traffic pollution or fine scale varying pollution, it does not matter that the correlations are too close to perform multipollutant models, as NO₂ is being used as an indicator (with an acknowledgement of the caveats).

Mortality. Similarly, a meta-analysis of single-pollutant models of long-term exposure to NO₂ and all-cause mortality could be used for the same (item d(iv) above) scenarios. For the reasons given before, we propose concentrating on all cause mortality. If desired, however, there would be less uncertainty in using a cardiovascular mortality concentration–response function than there would in using a NO₂ per se calculation. This is not only because there is no need to distinguish between NO₂ and PM (or at least traffic PM) in the epidemiology studies, but also because the toxicology that supports an effect of PM on cardiovascular outcomes also supports the epidemiology on a cardiovascular effect of traffic pollution, for which NO₂ is being used as a marker.

4. Summary

In a cost–benefit analysis, it can be helpful to group concentration–response functions according to their uncertainty. The cost–benefit analysis can start with a core set of functions and then be rerun with the addition of concentration–response functions in groups of increasing uncertainty. This can illustrate the degree to which the cost–benefit ratio depends on uncertain concentration–response functions. To illustrate the potential for such an exercise, the summary below is ranked on the basis of increasing uncertainty.

The recommendations are also summarized in Table 10, by both health impact assessment context (item d(i–iv) from section 1 above) and the level of uncertainty. The ranking by uncertainty has been applied to the NO₂ per se (central or sensitivity analysis) part of the table (three left-hand columns). There is, of course, uncertainty in using NO₂ as a marker for traffic, but the criteria for judging greater or lesser uncertainty will be different – for example, the presence or absence of multipollutant models will not be relevant. The uncertainty of assignment of health effects to one pollutant or another may be reduced in the future if biomarkers can be developed that are specific to mechanistic pathways of health effects that differ between pollutants and are convenient for routine measurement in population studies.

The concentration–response functions, listed by increasing uncertainty, are:

least uncertainty:

- respiratory hospital admissions, adjusted coefficient, using the averaging times as in the relevant studies;

increased degree of uncertainty:

- all-cause mortality (short term), adjusted coefficient, using the averaging times as in the relevant studies, increased degree of uncertainty due to the component of cardiovascular mortality, where there is an absence of a solid body of supporting chamber studies and toxicological evidence;
- bronchitic symptoms in asthmatic children, adjusted coefficient, long-term (year-to-year variations) from McConnell et al. (2003) – only study of long-term exposure to NO₂ and respiratory symptoms in children that adjusted for a wide range of other pollutants;

most uncertainty:

- cardiovascular admissions (short term), adjusted coefficient, using the averaging times as in the relevant studies – sensitivity analysis only, additional to quantification of PM;
- asthma prevalence, adjusted coefficient unavailable, annual average – for pollutant specific applications, use a sensitivity analysis of comparing effects of either black smoke or NO₂ (d(iii));
- all cause mortality (long term), it may not be possible to find an adjusted coefficient from a suitable study and the element of cardiovascular mortality adds extra uncertainty; for pollutant-specific applications with PM included, use only as a sensitivity analysis.

For the pollutant–outcome pairs in the category “most uncertainty”, there was increased difficulty controlling for confounding by other pollutants, less data or less available supporting clinical or toxicological evidence.

Table 10. Recommended pollutant outcome pairs by health impact assessment context and ranked by uncertainty

NO₂ per se, central analysis (d(i)) – that is, a likely effect of NO₂	NO₂ per se, sensitivity analysis (d(ii)) – that is, a possible effect of NO₂ additional to the effect of PM	NO₂ per se, sensitivity analysis, “what if either NO₂ or a PM metric” (d(iii)) (compare, but do not add)	Crude substitute for a PM effect, if PM data unavailable (d(iv))	Marker for traffic (with caveats)^a (better metric of primary PM than PM mass) (also (d(iv)))
<u>Respiratory hospital admissions (short term), adjusted coefficient preferable</u>	NA	NA	<i>Respiratory hospital admissions (short term), single-pollutant model</i>	Respiratory hospital admissions (short term), ^b single-pollutant model
NA	<i>Cardiovascular admissions, adjusted coefficient</i>	NA	<i>Cardiovascular admissions, single-pollutant model</i>	Cardiovascular admissions, single-pollutant model
<u>All-cause mortality (short term), adjusted coefficient preferable</u>	NA	NA	<i>All-cause mortality (short term), single-pollutant model (but may not be additional to effects of long-term exposure)</i>	All-cause mortality (short-term), single-pollutant model (but may not be additional to effects of long-term exposure)
<u>Bronchitic symptoms in asthmatic children (long term, year to year variations), adjusted coefficient</u>	NA	NA	[NO ₂ independent of several other PM metrics Bronchitic symptoms in asthmatic children could be used as a marker for organic carbon, but might not be a marker for diesel.]	Bronchitic symptoms in asthmatic children (long term, yearly variation element), single-pollutant models
NA	[Adjusted coefficients unavailable for asthma incidence and/or	<i>Asthma prevalence from within city studies, single-</i>	<i>Asthma prevalence from within city studies, single-</i>	Asthma prevalence within city, single-pollutant models

	prevalence studies]	<i>pollutant models</i>	<i>pollutant models</i>	
NA	<i>All-cause mortality (long term), adjusted coefficients</i>	<i>All-cause mortality (long-term), single-pollutant models</i>	<i>All-cause mortality (long term), single-pollutant models</i>	All-cause mortality (long term), single-pollutant models

^a The ratio of NO₂ to primary PM is changing over time.

^b It might be possible to use a model adjusted for PM_{2.5}, if examining the traffic pollution element is done separately from PM, in general.

Note. The following notations and conventions are used in this table: bold underline: least uncertainty; underline: some increased degree of uncertainty; italics: most uncertainty, increased difficulty in controlling for confounding, fewer studies, less supporting clinical or toxicological evidence; plain (straight, non-italic) text: traffic marker not on same scale of uncertainty as NO₂ per se; small font italics: rough substitute for PM, not on same scale of uncertainty as NO₂ per se, but uncertain; text in square brackets: notes; NA: not applicable.

Question C5

Is there any new evidence on the health effects of air emissions of arsenic, cadmium, mercury, lead and nickel (and their compounds) that would impact upon current target values?

Answer

Arsenic. Yes, there is some new evidence on the cancer risk of air emissions of arsenic, but it is contradictory in terms of the direction of risk. This new evidence is insufficient to have an impact on the current EU target value.

Cadmium. Yes, there is new evidence on the health effects of air emissions of cadmium. Reaching the present WHO air quality guidelines and EU target values does not prevent increasing cadmium levels in agricultural soil by air deposition, and thereby contributing to adverse effects on health in the general population. If the WHO air quality guidelines are reviewed, this new evidence should be considered.

Mercury. No, there is no new evidence on the health effects of air emissions of mercury that would have an impact on the current policy.

Lead. Yes, there is definitely new evidence on the health effects of air emissions of lead that would have an impact on the current limit value. This evidence shows that effects on the central nervous system in children and on the cardiovascular system in adults occur at, or below, the present standards in the WHO air quality guidelines and EU.

Nickel. Yes, there is some new evidence on the health effects of air emissions of nickel, but this would probably not have any significant impact on the risk estimate and the present target value.

Rationale

1. Arsenic

Present WHO air quality guidelines

Exposure to arsenic occurs in inorganic and organic forms, and in most cases oral intake predominates. The critical effect of inhalation of inorganic arsenic is considered to be lung cancer. The 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) used the unit risk of 1.5×10^{-3} , based on the risk of lung cancer (WHO Regional Office for Europe, 2000). Thus, a lifetime exposure to 6.6 ng/m^3 would cause an excess risk of 10^{-5} . For genotoxic carcinogens, such as arsenic, the 2005 global update of the WHO air quality guidelines did not present any guideline level. The evaluation was based mainly on three occupational smelter cohorts (Tacoma and Montana in the United States, and Ronnskar in Sweden). An updated pooled analysis of these cohorts was extrapolated and transformed into unit risk of 1.5×10^{-3} used by the

guidelines (Viren & Silvers, 1994). The EU target value for annual average arsenic in PM₁₀ is 6 ng/m³ (EU, 2005). Typical ambient arsenic concentrations in England are about 1 ng/m³ (EPAQS, 2009). Inhalation is a minor part of total exposure.

Later reviews

The United States Agency for Toxic Substances and Disease Registry reviewed the health risks of arsenic (ATSDR, 2007), but the Agency provides minimal risk levels for non-cancer end-points and did not publish any guideline for inorganic arsenic. There is a draft integrated risk information system (IRIS database) document from the EPA (2010b), and it does not propose any guideline limit (inhalation reference concentration, Rfc).

A United Kingdom expert panel evaluated the health risk of inhalation of inorganic arsenic (EPAQS, 2009). As a starting point, it used the midpoint of estimated cumulative exposure (125 µg/m³ multiplied by the number of years) in the lowest stratum in the Swedish smelter study with a significant increase in lung cancer. For a 40-year working life, this gave a lowest-observed-adverse-effect level (LOAEL) of 3 µg/m³. It was divided: by 10, to obtain a presumed no-observed-adverse-effect level (NOAEL); by 10, to obtain a longer exposure time for the general population; and by 10, to obtain the possible susceptible groups. With a factor of 1000, a guideline of 3 ng/m³ was proposed for the PM₁₀ fraction, as an annual average.

Recent studies

We found three studies published after 2005 that are relevant to the risk assessment for inhaled arsenic. The first, by Jones et al. (2007), found no significant association between cumulative arsenic exposure and lung cancer in a United Kingdom smelter, but did find significant associations when less weight was given to exposures that occurred long before the outcome. A statistically significant increase in the RR of lung cancer was found in the stratum with a mean (weighted) cumulative exposure to arsenic of about 1.5 mg/m³ multiplied by the number of years. This is higher than the LOAEL in the Swedish smelter study cited above, but the point estimates of strata with lower exposure are not incompatible with risk estimates in previous reviews.

The second study, by Lubin et al. (2008), reanalysed the Montana cohort and found a higher RR at high-intensity exposure to arsenic (for example, 0.6 mg/m³ for 5 years) compared with low-intensity exposure (for example, 0.3 mg/m³ for 10 years) at the same level of cumulative exposure. This makes sense in view of possible limitations in demethylation and/or detoxification ability. If it is true also for low-level exposure, arsenic in ambient air would be less risky than indicated in previous estimates made from occupational exposure. However, the conclusions are not generally accepted, and the results cannot be directly transformed into a unit risk estimate.

The third study, by Smith AH et al. (2009), compared the RRs of lung cancer of inhaling inorganic arsenic at the Tacoma smelter with the risk at ingestion of inorganic arsenic in drinking water in Chile, using arsenic concentrations in urine. They found that the excess RR of lung cancer versus urinary arsenic level was similar in the two cases. This would

indicate that the absorbed dose is carrying the risk, independent of whether it was inhaled or ingested. This is significant. If cancer risk estimates for arsenic in drinking-water (NAS, 2001), calculated as a function of arsenic concentrations in urine, could be transformed into air levels of arsenic, this would be an alternative way of estimating the cancer risk for the general population at low-level arsenic concentrations in ambient air. Using assumptions on absorbed arsenic by inhalation and ingestion, the United States National Academy of Sciences (NAS) estimate of the excess absolute risk of lung cancer would transform into a unit risk of 1×10^{-3} , very similar to the 1.5×10^{-3} estimate calculated from completely different data. However, one consequence of this notion is that we must then also consider urinary bladder cancer. It is generally accepted (NAS, 2001) that intake of arsenic in drinking water also increases the risk. The NAS estimates for the United States population for ingesting $10 \mu\text{g}$ arsenic per day from water for this site (based on Taiwanese data) is 12–23 per 10 000 (lifetime risk).

Evaluation

In the WHO air quality guidelines, a unit risk of 1.5×10^{-3} was proposed, based on extrapolations from cumulative exposure to arsenic in smelter cohorts. In the past decade, studies have suggested that the true unit risk could be *lower* or *higher* than that. Another technique, applying an unsafety factor of 1000 to the LOAEL in one of the smelter cohorts resulted in a guideline value of 3 ng/m^3 . In summary, the new evidence is insufficient to have an impact on the current EU target value.

2. Cadmium

Present WHO air quality guidelines

The main human exposure sources of cadmium are diet (higher uptake at low iron stores, making women usually more exposed than men) and smoking. The most well-known health effects of cadmium are kidney damage and toxic effects on bone tissue (osteomalacia and osteoporosis). Cadmium has been classified by the International Agency for Research on Cancer as a Group 1 human carcinogen, mainly due to the increased risk of lung cancer from occupational exposure to cadmium. In the WHO air quality guidelines (WHO Regional Office for Europe, 2000), the data behind the classification of cadmium as carcinogenic was considered to be complicated to interpret due to concomitant exposure to arsenic. Therefore, no unit risk of lung cancer, based on these studies, could be derived. The 2000 WHO Regional Office for Europe air quality guidelines noted that *average* kidney cadmium levels in Europe are very close to the critical level for renal effects. A further increase in dietary intake of cadmium, due to accumulation of cadmium in agricultural soils, must be prevented. Therefore, a guideline value of 5 ng/m^3 was set for cadmium in air (WHO Regional Office for Europe, 2000). This was also applied as an EU target value (EU, 2005). Present levels of cadmium in air are $0.1\text{--}1 \text{ ng/m}^3$ in rural areas, $1\text{--}10 \text{ ng/m}^3$ in urban areas, and higher than 10 ng/m^3 in some industrial areas (WHO Regional Office for Europe, 2007). Inhalation is a minor part of total exposure, but ambient levels are important for deposition in soil and, thereby, dietary intake.

Later reviews

WHO working group on long-range transboundary air pollution. A WHO Regional Office for Europe working group published the document *Health risks of heavy metals from long-range transboundary air pollution* (LRTAP) (WHO Regional Office for Europe, 2007). Emissions, depositions, air levels, and health risks were reviewed, including the impact of other factors (such as fertilizers and sewage). Information on the effects of low-level exposure to cadmium on markers of renal function and bone was updated. The working group mentioned two critical effects at low-level exposure to cadmium: excretion of low molecular weight proteins, due to tubular cell damage, and also osteoporosis. Studies on cadmium balance in topsoil in Europe indicated that the amount of input exceeds that of removal. The working group noted that several European studies in the late 1990s and the beginning of the 2000s showed effects on kidney and/or bone at environmental exposure levels for urinary cadmium as low as 0.5–2.0 µg/g creatinine (µg/gC). The working group proposed a LOAEL of 2 µg/gC. The evidence of lung cancer from inhalation of cadmium was considered to be rather weak. The margin of safety for adverse effects on the kidney and bone is very narrow for the European population and non-existent for sensitive subgroups, such as women with low iron stores. Since food represents more than 90% of the cadmium intake in non-smokers, and no decline has been shown, further efforts should be made to reduce cadmium emissions.

The United States Agency for Toxic Substances and Disease Registry reviewed the health risks of cadmium and recommended a minimal risk level for this hazardous substance (ATSDR, 2012). As a point of departure, the Agency selected the lower confidence limit for cadmium concentrations in urine, resulting in a 10% increase of the excretion of beta-2-microglobulin in one of the European studies – 0.5 µg/gC; it chose the study that found effects at the lowest cadmium concentration in urine. Based on a toxicokinetic model, long-term inhalation of 0.1 µg/m³, combined with the average dietary cadmium intake in the United States population, would result in cadmium concentrations in urine of 0.5 µg/gC. An uncertainty factor of 9 was applied to the cadmium concentration in air, and thus a minimal risk level of 10 ng/m³ was set.

The European Food Safety Authority (EFSA) reviewed cadmium in food (CONTAM, 2009). In a meta-analysis, it found the lower limit of the benchmark dose for a 5% increased prevalence of “elevated” beta-2-microglobulin to be 4 µg/gC for the cadmium concentration in urine. After adjusting for the interindividual variability of the cadmium concentration in urine, a critical concentration of cadmium in urine of 1 µg/gC was derived. EFSA also reviewed data on cadmium effects on bone: “studies summarized indicate a range of U-Cd [cadmium concentrations in urine] for possible effects on bone, starting from 0.5 µg/gC, which is similar to the levels at which kidney damage occurs”. EFSA also reviewed studies on cancer, including those based on environmental exposure (lung cancer: Nawrot et al., 2010; endometrial cancer: Akesson, Julin & Wolk, 2008). The data on hormone-related cancers were considered to need confirmation from other studies.

The Joint WHO/FAO Expert Committee on Food Additives (JECFA) used essentially the same studies on beta-2-microglobulin as did EFSA, but it used a slightly different statistical modelling technique and came to the conclusion that the point estimate for the break point for elevated beta-2-microglobulin was 5.2 µg/gC for cadmium concentrations in urine (JECFA, 2011). This was then transformed to a dietary intake of 0.8 µg/kg/day (lower confidence limit). The effects on bone were not considered.

The International Agency for Research on Cancer recently updated their evaluation of cadmium and cadmium compounds (IARC, 2012). The Agency found epidemiological support for lung cancer in humans from inhalation of cadmium and also found sufficient evidence of lung cancer in animals. Therefore, cadmium and cadmium compounds are carcinogenic to humans (Group 1), mainly based on the increased risk of lung cancer.

Recent studies

The above-mentioned reviews include literature up to 2006–2008. Thereafter, the published studies of major interest are of two types.

1. Some studies indicate that the associations between low-level exposure to cadmium and excretion of low molecular weight proteins shown in several other studies may not be due to cadmium toxicity. Instead, co-excretion of cadmium and proteins is more likely to be caused by physiological factors, such as varying reabsorption of cadmium and proteins in renal proximal tubules (Chaumont et al., 2012; Akerstrom et al., 2013).
2. Other published studies showed effects on bone at low-level exposure to environmental cadmium (Gallagher, Kovach & Meliker, 2008; Schutte et al., 2008; Wu, Magnus & Hentz, 2010; Nawrot et al., 2010; Thomas et al., 2011; Engström et al., 2011, 2012), although some did not find positive associations (Rignell-Hydbom et al., 2009; Trzcinka-Ochocka et al., 2010).

Evaluation

Research performed in the new millennium has indicated adverse effects of long-term dietary cadmium on kidney and bone at cadmium concentrations in urine commonly seen in most European countries – about 1 µg/gC. The WHO Regional Office for Europe air quality guidelines for 2000 is still valid; further increase of cadmium in agricultural soils must be prevented. The cadmium input in European agricultural soils is larger than the output, suggesting that the cadmium intake will not decrease. Overall, deposition from cadmium in air contributes typically about half of the cadmium input to soils. Present levels of cadmium in air are too high to obtain a cadmium balance in soils (WHO Regional Office for Europe, 2007). This should be taken into account when deciding whether the WHO air quality guidelines should be reconsidered.

3. Mercury (Hg)

Present WHO air quality guidelines

Humans are exposed to several mercury species, the two most important being elemental mercury vapour (Hg^0) and methylmercury (MeHg). Exposure to Hg^0 is mainly via inhalation of dental amalgam fillings (about 50% mercury by weight). In subjects without such fillings, exposure occurs by inhalation of ambient air, with a typical level of 1–3 ng/m^3 (total mercury, most of which is Hg^0), or indoor air, which may have ten times higher levels if occupied by people with amalgam fillings. Since about 80% of inhaled Hg^0 is absorbed, 3 ng/m^3 will result in an uptake of about 50 ng of mercury a day. The uptake from a person with a dozen amalgam fillings is usually about 100 times higher. The WHO air quality guidelines background document considered this as well as other routes of exposure.

Exposure to MeHg occurs by gastrointestinal absorption (about 90%), from dietary consumption of food – fish, in particular. In people without dental amalgam fillings, MeHg intake from fish is the predominant exposure route. It is well known that long-term occupational exposure to Hg^0 may affect the kidney and the central nervous system adversely. According to the WHO Regional Office for Europe air quality guidelines for 2000, LOAELs for occupational settings are air levels of 15–30 $\mu\text{g}/\text{m}^3$. After correcting for some measurement issues and inhaled volumes of air, an uncertainty factor of 20 was used, and the guideline value for ambient air was set at 1 $\mu\text{g}/\text{m}^3$. There is no EU target value for mercury in ambient air.

Later reviews

WHO CICAD. WHO published a review in the Concise International Chemical Assessment Documents (CICADs) series (WHO, 2003). Most information goes back, however, to the WHO International Programme on Chemical Safety document for mercury from 1991 and the Agency for Toxic Substances and Disease review from 1999. As the starting point, the authors of the review considered the subtle effects on the central nervous system of long-term occupational exposure to Hg^0 to be the result of about 20 $\mu\text{g}/\text{m}^3$ of Hg^0 . For inhalation by the general public, this corresponds to 5 $\mu\text{g}/\text{m}^3$, and an uncertainty factor of 30 resulted in a tolerable concentration of 0.2 $\mu\text{g}/\text{m}^3$.

Chapter in *Handbook on the toxicology of metals*. This handbook (from 2007), edited by Nordberg et al., is the so-called bible of metal toxicology. The 55-page chapter on mercury (Berlin, Zalups & Fowler, 2007) summarizes the information on mercury toxicity in a way similar to that of the CICAD document, but includes some more recent references – for example, a meta-analysis from 2002 on the neurobehavioral effects of exposure to Hg^0 in relation to urinary mercury levels (Meyer-Baron, Schaeper & Seeber, 2002). The evaluation of exposure–response is, however, similar to that of the WHO expert groups behind the WHO Regional Office for Europe air quality guidelines for 2000 and the WHO CICAD document from 2003. The Handbook also includes a separate chapter on interactions among metals.

WHO working group on LRTAP. The LRTAP document (WHO Regional Office for Europe, 2007) reviewed the data on emissions, deposition, air levels, and health risks in human beings. For health risks, the working group referred to occupational studies that indicated possible effects on the central nervous system after a long-term exposure to Hg^0 of about $20 \mu\text{g}/\text{m}^3$. The working group also discussed the risks of MeHg exposure, concluding that priority should be given to lowering the MeHg levels in fish. Reductions in mercury emissions to air are therefore warranted.

Recent studies

Some additional review papers (such as Clarkson & Magos, 2006) are either similar to the CICAD document or the Handbook chapter, or they are less complete than these. An EU review on the safety of dental amalgam has also been performed (SCENIHR, 2008). A large number of papers were published since the turn of this century, but none of them yields new evidence on exposure–response relationships. Important studies about very low-level exposure to Hg^0 include the two large randomized controlled trials of dental amalgam in children, which gave no support for adverse effects on the central nervous system (Bellinger et al., 2006; DeRouen et al., 2006).

Evaluation

The basis for determining a LOAEL for occupationally exposed workers has not changed. With regard to which so-called transformations should be used to go from occupational to environmental exposure, we consider those made by the CICAD document are more justified than those of the WHO air quality guidelines working group. However, there is no new evidence on the health effects of air emissions of mercury that would have an impact on the current policy.

4. Lead

Present WHO air quality guidelines

The WHO Working Group on Air Quality Guidelines noted that cognitive impairment has been shown in children at blood lead levels of 100–150 $\mu\text{g}/\text{l}$ and proposed a critical level of 100 $\mu\text{g}/\text{l}$. To assure that at least 98% of schoolchildren have blood lead levels of less than 100 $\mu\text{g}/\text{l}$, the median should not exceed 54 $\mu\text{g}/\text{l}$. The Working Group then assumed a baseline value of the (dietary) contribution to lead in blood of 20 $\mu\text{g}/\text{l}$ in uncontaminated areas. In air, $1 \mu\text{g}/\text{m}^3$ of lead was considered to increase the blood lead level by 50 $\mu\text{g}/\text{l}$ (19 $\mu\text{g}/\text{l}$ directly by inhalation and the rest indirectly). The Working Group aimed at a lead level in air that would not increase blood lead to a level above 50 $\mu\text{g}/\text{l}$, including the baseline; thus, lead in air should contribute no more than 30 $\mu\text{g}/\text{l}$. The target for lead in air was therefore set at $0.5 \mu\text{g}/\text{m}^3$. The same value has been adopted as the EU target value (EU, 2005).

Background levels in Europe are below $10 \text{ ng}/\text{m}^3$ (CONTAM, 2010), but they may be higher close to certain industrial sources. Levels have declined dramatically in cities after banning lead in gasoline; they were previously often on the order of $0.5\text{--}1.0 \mu\text{g}/\text{m}^3$ in large cities (WHO Regional Office for Europe, 2000, 2007). Inhalation of ambient air is a

minor part of total exposure, but ambient levels are important for contamination of soil and therefore for children's exposure.

Later reviews and recent original papers

Several reviews show that the adverse effects of lead in children and adults occur at much lower exposure levels than those that result in a blood lead level of 100 µg/l. The recent reviews – for example, by CONTAM (2010), by JECFA (2011) and by the United States National Toxicology Program (NTP, 2012) – use the pooled analyses by Lanphear et al. (2005). These reviews also consider the effects of exposure to lead on blood pressure and hypertension in adults, but here we put more focus on cognitive effects in children, since this will be the critical effect in deciding on target values.

The most recent review is the one by JECFA (2011). JECFA used a benchmark dose or central estimate of blood lead level of 20 µg/l for an intelligence quotient (IQ) cognitive function decrement of one point in children. The lower confidence limit was 10 µg/l. JECFA transformed blood lead level into dietary intake and chose a bilinear model that yielded a 0.5 IQ point decrease at 12 µg lead/day (0.6 µg/kg/day for a 20 kg child).

If we assume that the relationship in the WHO Regional Office for Europe air quality guidelines for 2000 is correct, lead in air of about 0.2 µg/m³ would increase blood lead levels by about 12 µg/l. Even inhalation alone at this level of lead in air would increase the blood lead level by about 4 µg/l.

For effects on blood pressure in adults, the estimate was an increase of systolic blood pressure of 0.3 mm Hg per increase in blood lead level of 10 µg/l. In the WHO Regional Office for Europe air quality guidelines for 2000, a lead level in air of 1 µg/m³ was assumed to increase the blood lead level by 16 µg/l in adults. Assuming a lead level in air of 0.2 µg/m³, this would transform into an increase (point estimate) of the blood lead level by about 3 µg/l and an increase of systolic blood pressure by about 0.1 mm Hg. We consider the above-mentioned effect on children's cognitive function to be more important.

Evaluation

It is obvious that the previous evaluation performed by the WHO Working Group on Air Quality Guidelines is not compatible with the evaluations done in later reviews, including those performed by the EU and WHO. The new evidence shows that effects on the central nervous system in children and on the cardiovascular system in adults occur at, or below, the present standards in the WHO air quality guidelines and EU.

5. Nickel

Present WHO air quality guidelines

The WHO Working Group on Air Quality Guidelines reported that ambient levels of nickel in air are about 1–10 ng/m³ in urban areas, but much higher in certain industrial areas. They noted that nickel is a human carcinogen (lung and nasal sinus) and referred to

an EPA unit risk estimate of $2.4\text{--}4.8 \times 10^{-4}$, depending on nickel compounds. The Working Group used data on cumulative exposure to nickel in Norwegian refinery workers (Andersen et al., 1996) as the basis for a transformation to a unit risk for environmental exposure of 3.8×10^{-4} , corresponding to the excess lifetime lung cancer risk of 10^{-5} at 25 ng/m^3 . It is unclear how this calculation was performed. The EU target value is 20 ng/m^3 (EU, 2005). Ambient levels are usually below 5 ng/m^3 , but are higher close to certain metal industries (EPAQS, 2009). Inhalation is a minor part of total exposure.

Later reviews and recent original papers

ATSDR (2005) refers to EPA data from 1986 and to the EPA evaluation of a unit risk of $2.4\text{--}4.8 \times 10^{-3}$ – that is, ten times higher than that of the WHO air quality guidelines.

Although not a formal review, Lippmann et al. (2006) report findings in mice exposed to concentrated ambient particles, as well as their findings when doing new analyses on previous time series analyses of mortality and PM_{10} in NMMAPS. Moreover, previous literature on the cardiovascular effects of nickel is summarized. Lippmann et al. found effects on heart rate variability related to the content of nickel, vanadium, chromium and iron in $\text{ApoE}^{-/-}$ mice exposed to concentrated ambient particles, and of the effects of nickel and vanadium on the risk estimate for PM_{10} in NMMAPS. In both cases the effect of nickel was the strongest.

The United Kingdom Expert Panel on Air Quality Standards (EPAQS, 2009) used an exposure–response model from Seilkop & Oller (2003) and Norwegian studies by Grimsrud et al. (2002, 2003) and came to the conclusion that there is an increased risk of cancer for occupational exposure for 40 years at a level of $20 \text{ }\mu\text{g/m}^3$ of nickel in air. Using an uncertainty factor of 1000, the Panel recommended a guideline value (annual average) of 20 ng/m^3 .

The International Agency for Research on Cancer (IARC, 2012) updated the epidemiological data of occupational cohorts exposed to nickel (latest reference 2009). The risk estimates are similar to those used by the United Kingdom Expert Panel on Air Quality Standards. According to the International Agency for Research on Cancer, nickel is a Group 1 human carcinogen.

Haney et al. (2012) used the Grimsrud cohort and an older United States cohort to assess the cancer risk and estimated the unit risk to be 1.7×10^{-4} .

After the above-mentioned paper by Lippmann et al. (2006), several reports followed up on the contribution of nickel to the adverse effects on health of fine PM and found some support for the hypothesis that fuel combustion in power generation (which usually emits nickel and vanadium) could contribute to the risk of cardiovascular disease (Bell et al., 2009b; Zhou et al., 2011; Ostro et al., 2011; Suh et al., 2011). The strongest indication is from a recent case-crossover study on stroke by Mostofsky et al. (2012), who found

nickel to be the element that showed the strongest (although non-significant) association with stroke incidence, surpassed only by black carbon.

As indicated above, the WHO air quality guideline for nickel is based on its carcinogenicity. Nickel is a normal constituent of ambient air and one of the (many) components suspected to carry the risk of fine PM.

Evaluation

There is some updated occupational epidemiology on nickel refinery workers since the review by the WHO Working Group on Air Quality Guidelines for 2000. The impression is, however that this new data will not change the previous unit risk estimate substantially. Data on the effect of ambient nickel levels on cardiovascular risk are yet too limited to permit their use in WHO air quality guideline standards.

Question C6

Is there any new evidence on health effects due to air emissions of polycyclic aromatic hydrocarbons that would impact upon current target values?

Answer

Some polycyclic aromatic hydrocarbons (PAHs) are potent carcinogens, and they are often attached to airborne particles, which may also play a role in their carcinogenicity. As PAHs are carcinogenic by a genotoxic mode of action, their levels in air should be kept as low as possible. There is new evidence linking PAH exposure to cardiovascular end-points, but at present these effects of PAH exposure cannot be separated from the effects of particles and therefore cannot impact on the target values. Studies on early biological effects of PAH exposure based on biomarkers, including PAH-DNA adducts, in general populations of children and adults also suggest a range of potential non-carcinogenic effects. Overall, there is no new evidence from which to propose a new target value. However, it should be noted that, based on previous literature, the existing target value of 1 ng/m^3 of benzo[*a*]pyrene is associated with the lifetime cancer risk of approximately 1×10^{-4} .

Rationale

In the context of air pollution, PAHs containing two or three rings are almost entirely present in the vapour phase. Those containing five rings or more (including benzo[*a*]pyrene) are found predominantly in the particle phase. Four-ring compounds are also particle bound, but have more seasonal variability between phases. The majority of particle-bound PAHs are associated with small particles – that is, smaller than $2.5 \mu\text{m}$ (EC, 2001).

PM, of which the most studied type is diesel exhaust particles, consists of elemental carbon to which is bound inorganic (such as metals) and organic compounds. The 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) concluded that the health effects of diesel exhaust particles and, possibly, other types of particles are mediated by chemicals adsorbed on to their surfaces, rather than due to the particle core, and that, among these chemicals, the organic constituents – in particular the PAHs or their nitro- or oxy-derivatives – are likely to be toxicologically active.

While a high burden of particles almost completely free of organic mutagens was able to produce tumours in rat lung after chronic inhalation exposure, the carcinogenic potency of particles through non-genotoxic mechanisms at much lower concentrations in ambient air is not known. Under such conditions, the genotoxic action of PAHs and derived mutagenic substances attached to the particles might well be a more significant risk factor (WHO Regional Office for Europe, 2000). However, many studies that have considered

exposure to, and the health effects resulting from, PM have not specifically addressed the issue of the concentrations or influence of particle-bound PAHs.

The major anthropogenic emission sources of PAHs are: domestic, mobile, industrial and agricultural. Domestic sources are mainly heating and cooking based on the combustion of fossil fuels. Mobile sources are from transport reliant on combustion engines, either gasoline or diesel fuelled. Catalytic converters for gasoline engines markedly reduce PAH emissions (by up to 90%); equivalent devices for diesel engines also reduce PAH emissions, but not to the same extent as for gasoline engines. For both fuels, an additional source of PAHs in the exhaust is the presence of PAHs in the fuel itself. In some southern European cities, motor scooters with two-stroke engines (fuelled by a mixture of petrol and oil) may represent a significant source of PAH emissions. Industrial sources of PAHs (such as aluminium, steel and coke production; commercial heat and power; waste incineration; creosote, bitumen and asphalt production; and petrochemical and related industries) are comparatively well understood and are being regulated increasingly. Agricultural sources (such as from burning stubble) are more variable, but may nevertheless contribute significantly to PAH levels at certain locations.

Most of the carcinogenic potential of PAHs resides with four- to seven-ringed compounds. The relevant exposure route for the lung is via inhalation of PAHs associated with airborne particles. The unit risk (lifetime exposure to a mixture represented by 1 ng/m³ benzo[*a*]pyrene), based on a number of occupational studies, is in the range of 80–100 x 10⁻⁶. The WHO estimate of a unit risk quoted by the EC as 8.7 x 10⁻⁵ (established by WHO in 1987) results in the increased risk associated with benzo[*a*]pyrene concentrations of 0.01, 0.1, and 1.0 ng/m³ being 1 x 10⁻⁶, 1 x 10⁻⁵ and 1 x 10⁻⁴, respectively (EC, 2001). This risk estimate (8.7 x 10⁻⁵) is as stated by WHO in both 2000 and 2010 (WHO Regional Office for Europe, 2000, 2010), although in both documents the excess lifetime risks of 1 x 10⁻⁶, 1 x 10⁻⁵ and 1 x 10⁻⁴ are given as 0.012, 0.12 and 1.2 ng/m³ benzo[*a*]pyrene, respectively. The current EU guideline value for benzo[*a*]pyrene is 1.0 ng/m³, which equates with a lifetime cancer risk of 1 x 10⁻⁴ (EC, 2012). In 1999, the United Kingdom Expert Panel on Air Quality Standards recommended a lower value for the air quality standard – namely, 0.25 ng/m³ – as an annual average, deriving this figure from consideration of the lower end of the range of concentrations with observable effects in occupational exposure scenarios (DEFRA, 1999).

Even in the absence of new evidence, the acceptability of the level of risk associated with the current target value should be reviewed and discussed. The current lifetime cumulative risk for benzo[*a*]pyrene causing cancer (1E-04) that is associated with the current guideline (1 ng/m³) is somewhat high. According to the EPA (EPA Region 8, 2013)

The level of total cancer risk that is of concern is a matter of personal, community, and regulatory judgment. In general, the EPA considers excess cancer risks that are below about 1 chance in 1 000 000 (1×10⁻⁶ or 1E-06) to be so small as to be negligible, and risks above 1E-04 to be sufficiently large that some sort of remediation is desirable. Excess

cancer risks that range between 1E-06 and 1E-04 are generally considered to be acceptable (see Role of the Baseline Risk Assessment in Superfund Remedy Selection Decisions (Memorandum from D. R. Clay, OSWER 9355.0-30, April 1991), although this is evaluated on a case-by-case basis and EPA may determine that risks lower than 1E-04 are not sufficiently protective and warrant remedial action.

In discussing the use of a single indicator carcinogen (benzo[*a*]pyrene) to represent the carcinogenic potential of the complex mixture of PAHs, the 2000 WHO air quality guidelines for Europe (WHO Regional Office for Europe, 2000) states:

BaP [benzo[*a*]pyrene] alone will probably underestimate the carcinogenic potential of airborne PAH mixtures, since co-occurring substances are also carcinogenic (WHO, 2000). Nevertheless, the well-studied common constituent of PAH mixtures, BaP, was chosen as an indicator, although the limitation and uncertainties in such an approach were recognized.

Although the need to analyse the levels of other carcinogenic PAHs has been emphasized (Boström et al., 2002), nevertheless a recent analysis (Delgado-Saborit, Stark & Harrison, 2011) concludes that “the relative contribution of BaP [benzo[*a*]pyrene] to the PAH overall carcinogenic potency is similar indoors (49%), outdoors (54%) and in the smelter environment (48%)”, suggesting the suitability of benzo[*a*]pyrene as a marker for the carcinogenic potentials of PAH mixtures, irrespective of the environment.

Dibenzo[*a,l*]pyrene is one of the most potently carcinogenic PAHs, although it has not been tested for carcinogenicity by inhalation. Estimates of its potency (potency equivalency factor) relative to benzo[*a*]pyrene vary, according to Delgado-Saborit, Stark & Harrison (2011), from 1 to 100. In most analyses, it is estimated to be the second contributor to the carcinogenicity of PAH mixtures (between 3% and 27%, compared with 45–73% for benzo[*a*]pyrene), although in one analysis it is estimated to contribute 77%, with benzo[*a*]pyrene second most important (17%). The United Kingdom PAH Monitoring and Analysis Network has reported that the ratio of dibenzo[*a,l*]pyrene to benzo[*a*]pyrene is relatively constant between sites with different dominating sources, at an average of 0.32:1.00 (Conolly, 2009). However, in a recent Italian study (Menichini & Merli, 2012), the ratio was lower (0.022:1.000).

In view of these analyses, there would not appear to be any advantage in diverging from the current policy of using benzo[*a*]pyrene as the single indicator compound for PAHs.

In 2005, the International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans reclassified benzo[*a*]pyrene as a Group 1 carcinogen (carcinogenic to humans), based on mechanistic evidence summarized as follows (IARC, 2010).

The complete sequence of steps in the metabolic activation pathway of benzo[*a*]pyrene to mutagenic and carcinogenic diol epoxides has been demonstrated in experimental animals, in human tissues and in humans. Following exposure, humans metabolically activate benzo[*a*]pyrene to benzo[*a*]pyrene diol epoxides that form DNA adducts: the

anti-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine adduct has been measured in populations (e.g. coke-oven workers, chimney sweeps) exposed to PAH mixtures that contain benzo[*a*]pyrene. The reactive *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide induces mutations in rodent and human cells. Mutations (G→T transversions) in the *K-ras* proto-oncogene in lung tumours from benzo[*a*]pyrene-treated mice are associated with *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine adducts. Similar mutations in the *K-RAS* proto-oncogene and mutations in *TP53* were found in lung tumours from nonsmokers exposed to PAH-rich products of coal combustion that are known to contain benzo[*a*]pyrene (as well as many other PAHs). In an in-vitro study, the codons in the tumour-suppressor gene *TP53* that are most frequently mutated in human lung cancer were shown to be targets for DNA adduct formation and mutations induced by benzo[*a*]pyrene.

In addition, evaluation by the International Agency for Research on Cancer in 2011 of bitumen fumes, which contain PAHs, resulted in the following classifications: occupational exposures to oxidized bitumens and their emissions during roofing are “probably carcinogenic to humans” (Group 2A); occupational exposures to hard bitumens and their emissions during mastic asphalt work are “possibly carcinogenic to humans” (Group 2B); and occupational exposures to straight-run bitumens and their emissions during road paving are “possibly carcinogenic to humans” (Group 2B) (Lauby-Secretan et al., 2011).

Most recently, in June 2012, the International Agency for Research on Cancer evaluated diesel-engine and gasoline-engine exhausts and classified diesel-engine exhaust as “carcinogenic to humans” (Group 1). Thus far, these findings are reported in a brief summary (Benbrahim-Tallaa et al., 2012), which makes no specific evaluation of PAHs other than to mention their presence in the gas and particle phase. Thus, at the present time, it is not possible to derive any specific association from this evaluation of PAHs.

In a study of the relationship between PAH exposure and ischaemic heart disease, a positive correlation was found between mortality from this disease and both cumulative and average exposure indices for benzo[*a*]pyrene (Burstyn et al., 2005). For average exposures of 273 ng/m³ – that is, occupational exposures considerably higher than environmental levels – the RR was 1.64 (95% CI: 1.13–2.38). PAHs were also associated with increased systemic inflammation, which explained the association with quasi-ultrafine particle mass from traffic emission sources, more so than other organic components of PM (Delfino et al., 2010b). Another study found an association between PM, particle-bound organic compounds (including PAHs) and adverse health symptoms in survivors of myocardial infarctions (Kraus et al., 2011). However in these studies, the effects of PAHs are not fully separated from the effects of the PM to which they are bound.

A number of recent studies have examined the effects of PAH exposure on child development. Levels of PAH-DNA adducts in cord blood have been found to be associated with higher symptom scores of anxiety and depression measured at 4.8 years (Perera et al., 2011). In the same cohort, prenatal exposure to benzo[*a*]pyrene measured from maternal personal air monitoring (at a median level of 2.27 ng/m³), and also cord

blood adduct levels, were associated with these effects, as well as attention problems at age 6–7 years (Perera et al., 2012). Similar findings come from a study of children in Poland (Edwards et al., 2010), where high PAH exposure in utero also restricted fetal growth (Choi et al., 2012). Effects on fetal development were exacerbated by obesity in African-American women (Choi & Perera, 2012).

The carcinogenic and toxicological properties of PAHs have been extensively investigated and reviewed (Luch, 2005). Their mode of action is genotoxic, and their DNA adducts elicit nucleotide excision repair mechanisms. They also induce aberrant gene expression and cell signalling and epigenetic effects that may contribute to their carcinogenic and other toxicological properties.

The utility of biomarkers for monitoring human exposure to PAHs was discussed in the 2000 WHO air quality guidelines for Europe (WHO Regional Office for Europe, 2000). Those biomarkers specific for PAHs include urinary 1-hydroxypyrene and the measurement of PAH-protein and DNA adducts by immunoassay, while the ³²P-postlabelling assay for DNA adducts is more sensitive, but less specific. Overall, different biomarkers have been validated to varying extents (Gallo et al., 2008). Measurement of cytogenetic damage, including chromosomal aberrations, is not particularly sensitive for measuring environmental PAH exposure. A recent meta-analysis of occupational exposure to PAHs has concluded that micronucleus formation, chromosomal aberration and sister chromatid exchanges in peripheral blood lymphocytes are all significantly higher in workers, with ranges of exposures (where known) higher than the current target environmental level (Wang et al., 2012).

Although large scale studies have validated chromosomal aberrations as biomarkers of cancer risk (Bonassi et al., 2008), the methods would not be specific if applied to health effects of environmental PAH exposure and would not distinguish other routes of exposure (such as dietary). Likewise, for DNA adducts, recent studies have validated these as biomarkers of lung cancer risk for smokers (Veglia et al., 2008); however, for exposures to PAHs, dietary exposures would also contribute to the adducts detected. Furthermore, the relationship between adduct levels (such as in white blood cell DNA) and ambient air levels of PAHs is non-linear, with evidence of saturation (that is, plateau) at higher levels of exposure.

Question C7

Is there any new evidence on the health effects of short term (less than 1 day) exposures to SO₂ that would lead to changes of the WHO air quality guidelines based on 10 minute and daily averaging periods or the EU's air quality limit values based on hourly and daily averaging periods?

Answer

There are no new respiratory chamber studies that would change the 10-minute guideline of 500 µg/m³, previously based on these types of studies. However, a reanalysis of the previous literature has found a small difference between responders and non-responders at 572 µg/m³ (0.2 ppm) (not statistically significant after control for multiple comparisons), the starting point for deriving the previous guideline. Thus, while the currently available statistical analysis suggests that the starting point does not need to be changed, a small increase in the safety factor from the current value of 1.15 might be justified when the time comes to reconsider the guideline, as the small (though non-significant) difference between responders and non-responders at this concentration increases the uncertainty as to whether this is a no-effect level or a minimal-effect level. Should further evidence confirm this difference, then the starting point may need to be changed in the future.

The 24-hour average guideline was based on the low end of the concentration ranges used in the time-series studies and on the Hong Kong intervention study. The time-series evidence continues to accumulate and continues to be inconsistent when adjusted for other pollutants for many (but not all) outcomes – for example, it is consistent for asthma admissions. The results of the original Hong Kong intervention study remain as a reduction in mortality for a reduction in pre- and post-intervention exposure to SO₂ independent of PM₁₀, although a more recent report suggests more difficulty in disentangling the effects of the reductions in SO₂ from reductions in other constituents, such as nickel or vanadium. The new studies are at a similar range of concentrations as the previous studies, so the 24-hour average guideline does not need to be changed if the same method (using a concentration at the low end of the range of concentrations) is followed for setting the guideline.

Rationale

A literature search – for sulfur dioxide or sulphur dioxide, toxicity and health, some author and study searches, consultation of other documents that include reviews and reports (EPA, 2008a) and consultation of APED – indicates that a large number of new studies have been published since 2004 (the literature cut-off date for the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006)). The text below concentrates on the direct health effects of SO₂, but indirect effects are also possible. SO₂ is an important prerequisite for urban nucleation to form particles smaller than 0.02 microns (see Question C8), although only exceedingly low concentrations are

required to allow sufficient formation of sulfuric acid, to initiate nucleation. The health effects of these nanoparticles are poorly understood. The text below also concentrates only on short-term exposures to address the exact question posed.

Chamber study evidence

The WHO guideline value of $500 \mu\text{g}/\text{m}^3$ for a 10-minute average is based on evidence from human chamber studies that show reductions in FEV1 and increases in airway resistance and symptoms (WHO Regional Office for Europe, 2006). A review was recently published (Johns & Linn, 2011) following consideration of chamber study evidence by the EPA in 2008 (EPA, 2008a). The Johns & Linn review only identified two papers published since 2004 (see below) and concluded that the older studies continued to have an integral role in assessing the respiratory effects of SO_2 . As a result, the key statements in the review reflect very closely those made in the WHO guidelines.

A paper worth close examination by Johns, Svendsgaard & Linn (2010) pooled data on individuals from several key studies to analyse an overall concentration–response relationship in asthmatics, with a particular emphasis on responders and non-responders. The EPA (2008a) estimated that 5–30% of asthmatics during 5–10 minutes of exercise could experience moderate or greater decrements in lung function at 0.2 ppm to 0.3 ppm SO_2 . The Johns, Svendsgaard & Linn (2010) analysis showed a clear concentration–response relationship between $572 \mu\text{g}/\text{m}^3$ (0.2 ppm) and $2860 \mu\text{g}/\text{m}^3$ (1 ppm) (the maximum concentration examined). This provides a more formal basis for the conclusions in the WHO guidelines. It also provides clearer evidence that the response at lower doses can be split between responders and non-responders (responders being defined at higher doses). Responders showed no significant change in airway resistance and a minor 5% decrease in FEV1 that was not significant after correction for multiple comparisons at $572 \mu\text{g}/\text{m}^3$ (0.2 ppm). This does not suggest a change from the use of $572 \mu\text{g}/\text{m}^3$ (0.2 ppm) as the starting point for setting the current guideline, although further statistical modelling to consider the possible location of a threshold might be helpful.

However, because a separation in the response of responders and non-responders was still apparent at $572 \mu\text{g}/\text{m}^3$ (0.2 ppm), even if not significant with correction for multiple comparisons, it increases the uncertainty as to whether this is a no-effect level or a minimal-effect level. In addition, the studies only involve mild asthmatics. The safety factor applied to the $572 \mu\text{g}/\text{m}^3$ (0.2 ppm) level in the current guideline was only 1.15. Given the uncertainties just raised, it should be considered, in a future reconsideration of the guidelines, whether a larger safety factor would be appropriate. Further studies to give a larger pooled sample size would be needed to confirm whether or not there is a real difference between responders and non-responders at this concentration. If this was confirmed, the starting point for the guideline would need to be changed.

The only other studies are: one showing no pulmonary response in healthy adults below 2 ppm (van Thriel et al., 2010); and one showing a reduction in cardiac vagal control (root mean square of the successive differences (RMSSD)) in 20 normal subjects, but not

those with stable angina, 4 hours (but not 1 hour) after exposure to 572 $\mu\text{g}/\text{m}^3$ (0.2 ppm) SO_2 for 1 hour (Routledge et al., 2006). Baroreflex sensitivity was also reduced. The implications of such changes in healthy subjects are unclear, and the EPA noted that the absolute values of the RMSSD did not differ significantly from subjects exposed to air (although the change from baseline did). Of the stable angina patients, 70% were on beta blockers, which may have protected them from adverse changes. More studies are needed to confirm this finding.

Panel studies

The EPA considered the possibility that there was some evidence for SO_2 having an effect on heart rate variability, but that the number of studies was limited. Our search did not pick up any further panel studies on heart rate variability. Also, the EPA considered evidence on arrhythmias to be inconsistent. A study that found a non-significant positive association between SO_2 and activation of defibrillators does not change this conclusion (Anderson et al., 2010). The EPA concluded the number of studies was too limited to come to a conclusion about inflammatory markers in the blood. Only one further study, suggesting increased levels of serum C-reactive protein in children, has been published since (Shima, 2007). Goldberg et al. (2008) found positive and statistically significant associations of SO_2 with reduced oxygen saturation and increased pulse rate in congestive heart failure patients. Briet et al. (2007) (not considered by the EPA) found that 5-day average SO_2 reduced endothelium-dependent brachial artery flow-mediated dilatation in healthy male subjects along with nitric oxide, but not with other pollutants, such as NO_2 and PM.

A multicity study by Schildcrout et al. (2006) was highlighted as part of the established evidence for an effect of SO_2 on asthma symptoms in children (EPA, 2008a). This showed an effect on asthma symptoms, but not on rescue inhaler use. The risk was increased in joint models with NO_2 and carbon monoxide (which were found to be more important pollutants in this study) and unchanged in a joint model with PM_{10} (with only a marginal loss of statistical significance). PM_{10} had no effect in this study. The EPA regarded the evidence as more mixed for symptoms in adults and limited for lung function in adults and children. More recent studies have found an effect of SO_2 , at least in single-pollutant models, for respiratory symptoms (Zhao Z et al., 2008 for indoor not outdoor SO_2 ; Moon et al., 2009) and lung function in children (Chang et al., 2012; Liu et al., 2009), the latter not robust to control for $\text{PM}_{2.5}$. In adults, increased respiratory symptoms were shown in healthy adults returning to an island after a volcanic eruption (Ishigami et al., 2008; Iwasawa et al., 2009) at high concentrations of SO_2 ,¹⁹ but increases were statistically insignificant in chronic obstructive pulmonary disease patients (Peacock et al., 2011) at lower concentrations (maximum: 75 ppb for a 24-hour average). Possible declines in lung function were found in asthmatic adults (Canova et al., 2010) (maximum: 5 ppb for a 24-hour average), but not in chronic obstructive pulmonary disease patients (Peacock et al., 2011) or healthy adults on the volcanic island (Iwasawa et al., 2009).

¹⁹ Above a 0.1 ppm hourly average or above a 2 ppm 1-minute average within each hour (Ishigami et al., 2008); 4–7.5% of hourly average exceeding 0.1 ppm; maximum 5-minute average of 5–17 ppm (Iwasawa et al., 2009).

These more recent studies do not represent any major shift in evidence since the EPA review.

Time series evidence

The 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) noted that observational time-series studies had reported numerous mortality and morbidity risk estimates for SO₂ over the preceding decade. It was considered that the consistency of the association of SO₂ with health outcomes appeared to be less than that for PM, but that the magnitude of the estimated risks was often comparable with that of PM.

Short-term exposure and mortality

Since the publication of the 2005 global update of the WHO air quality guidelines, Anderson et al. published a peer-reviewed research report that contains meta-analyses of time-series studies, based on studies up until 2006 (Anderson et al., 2007). In single-city studies, positive and statistically significant associations with SO₂ were generally found for all-cause, cardiovascular, cardiac and respiratory mortality in single-pollutant models. While the majority of the single-city studies are from before 2004, there are a few post-2004 studies included in some of the summary estimates described below (Jerrett et al., 2004, Penttinen, Tiittanen & Pekkanen, 2004). Most estimates showed significant heterogeneity, except those for cardiorespiratory mortality and mortality from lower respiratory infections, but there was also significant heterogeneity for the main mortality end-points for PM₁₀. Adjustment for publication bias, where shown (all except cardiorespiratory, cardiac and stroke mortality), reduced the size of the summary estimates, but they remained positive and statistically significant. The size of the estimates was only slightly lower than those for PM₁₀.

There was substantial overlap between the multicity studies reviewed for the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006) and for the Anderson et al. report (Anderson et al., 2007), but the latter covered more studies (none published after 2004). Again there were positive, statistically significant associations in single-pollutant models with all-cause, cardiovascular, cardiac and respiratory mortality, but those associations tested in multipollutant models were reduced by control for other pollutants, often substantially, and often lost statistical significance. Multipollutant models in single-city studies were not reviewed in this report.

The EPA view, published in 2008 (EPA, 2008a), covered much of the same material, but also included the Public Health and Air Pollution in Asia literature review (HEI, 2004), which found that a meta-analysis of time-series studies of SO₂ and mortality in Asia gave similar results to those of European multicity studies. Overall, the EPA considered that there was suggestive evidence of a causal relationship (consistent in single-pollutant models, more uncertain after adjustment for co-pollutants). The Hong Kong Intervention study (Hedley et al., 2002) was noted for the effect of a change in SO₂ on mortality, in the absence of a change in PM₁₀; also noted was that this change in sulfur in fuel may have

included changes in heavy metal content (reported reference: Hedley et al. (2006); now available in journal form: Hedley et al. (2008)).

The Hong Kong Intervention has now been studied in more detail (Wong et al., 2012). The decrease in SO₂ concentrations between the pre- and post-intervention periods was accompanied by decreases in NO₂ and increases in ozone. There were also decreases in metals (aluminium, iron, manganese, nickel, vanadium, lead and zinc) associated with particles, of which the decreases in nickel and vanadium were most consistent. While nickel and vanadium were associated with mortality in general terms, it was not possible to show a clear link between changes in their concentrations being associated with the intervention and with changes in their effect on mortality after (compared with before) the intervention (although there was a decline). In this more detailed study, SO₂ only showed a decrease in the excess risk of respiratory mortality (not statistically significant), but also showed an increase in the excess risk of all-cause (not statistically significant) and cardiovascular mortality after (compared with before) the intervention. In the overall study (irrespective of the intervention), the effects of SO₂ on mortality were not stable to adjustment for nickel and vanadium. In summary, while the intervention was still beneficial, a more detailed study suggests that identifying the responsible pollutant is difficult.

APED, used to prepare the review by Anderson et al. (2007), has now been updated to 2009 for papers on SO₂. The database uses a comprehensive literature searching strategy, with sifting for study quality criteria. The database indicates seven new studies (Cakmak, Dales & Vidal, 2007; Filleul et al., 2006a; Kowalska et al., 2008; Lee, Son & Cho, 2007b; Tsai et al., 2003; Wong et al., 2008; Yang et al., 2004), for all-cause mortality, all ages, all-year and 24-hour average SO₂, that had quantitative estimates and did not overlap with other studies (see Table 11). The literature search identified a further two studies meeting these criteria (Rajarithnam et al., 2011; Rabczenko et al., 2005) and a further paper has been identified since (Chen et al., 2012c). Most of the studies showed positive associations (8 of 10) of which five were statistically significant. The range of the central estimates (-1.4–3% per 10 µg/m³) were all within the range of the 144 previous estimates (-4.63–6.4% per 10 µg/m³). Although two Asian study estimates (Wong et al., 2008, Lee, Son & Cho, 2007b) were higher than the current summary estimate, it is unlikely that this would change an updated summary estimate much, given the large number of studies already in the meta-analysis.

Table 11. Selected quantitative estimates for SO₂ and mortality

Study type	Estimates for all-cause mortality, all ages, all year, per cent increase per 10 µg/m ³ for SO ₂ 24-hour average		
	Studies highlighted in WHO Regional Office for Europe (2006) guidelines	Anderson et al. (2007), additional multicity studies, ^a single-city meta-analysis	Others (more recent or not previously covered)
Multicity	0.4 (95% CI: 0.3–0.5) APHEA 1 Katsouyanni et al. (1997)	0.4 (95% CI: 0.2–0.5) 7 Korean cities Lee et al. (2000)	1.0 (95% CI: 0.8–1.3) 4 Asian cities Wong et al. (2008)
Multicity	0.5 (95% CI: 0.1–0.9) EMECAM Ballester et al. (2002)	1.5 (95% CI: 1.1–1.9) 8 Italian cities Biggeri, Bellini & Terracini (2001)	0.4 (95% CI: 0.1–0.7) 4 Polish cities Rabczenko et al. (2005)
Multicity	0.2 (95% CI: 0.1–0.3) NMMAPS Samet et al. (2000)	0.7 (95% CI: 0.4–1.0) 9 French cities Le Tertre et al. (2002)	0.75 (95% CI: 0.5–1.0) 17 Chinese cities Chen et al. (2012c)
Multicity	1.2 (95% CI: 0.8–1.7) 11 Canadian cities Burnett, Cakmak & Brook (1998)	--	Range of central estimates for new studies: ^b -1.4% to 3%
Meta-analyses	0.4 (95% CI: 0.2–0.5) non-GAM meta-analysis 0.4 (95% CI: 0.3–0.5) GAM meta-analysis Stieb, Judek & Burnett (2002, 2003)	0.5 (95% CI: 0.4–0.5) Single-city meta-analysis (including NMMAPS) 0.4 (95% CI: 0.3–0.5) adjusted for publication bias Anderson et al. (2007)	0.5 (95% CI: 0.3–0.7) 11 Asian city meta-analysis HEI (2004)

^a This excludes those in the same countries as the multicity studies highlighted in the WHO column.

^b Sources: Cakmak, Dales & Vidal (2007); Filleul et al. (2006a); Kowalska et al. (2008); Lee et al. (2007b); Rabczenko et al. (2005); Rajarathnam et al. (2011); Tsai et al. (2006b); Wong et al. (2008); Yang et al. (2004).

In a study in Santiago, Chile, the SO₂ estimate generally remained stable after adjustment for PM₁₀, ozone and carbon monoxide (Cakmak, Dales & Vidal, 2007), and a negative association in Delhi, India, was unchanged by adjustment for PM₁₀, with and without NO₂ (Rajarathnam et al., 2011). The HEI report collating four Asian city studies (Wong et al., 2010b) found the estimate remained stable after adjustment for PM₁₀ and ozone, but not for NO₂, with the exception of Bangkok, where the estimate was reduced by both PM₁₀ and NO₂. In the study of 17 Chinese cities (Chen et al., 2012c), the estimate was reduced, but remained positive and statistically significant when controlled for PM₁₀; the reduction on adjustment for NO₂ was substantial, and the estimate lost significance. There were too few multipollutant-model studies in the earlier Asian city meta-analysis to draw an overall conclusion (HEI, 2004). This does not change the previous view (Anderson et al., 2007; WHO Regional Office for Europe, 2006) that estimates for all-cause mortality could be sensitive to adjustment for other pollutants. It is possible that the short sharp peaks of SO₂ mean it is more subject to measurement error, which can affect multipollutant models. However, Zeka & Schwartz (2004) found that, using a statistical

technique for multipollutant adjustment less subject to measurement error, the SO₂ estimate was small and was not statistically significant.

The report on four Asian cities (Wong et al., 2010b) examined the shape of the concentration–response function with mixed results (2 of 4 linear), but none of them examined the shape after control for other pollutants.

Short-term exposure and respiratory hospital admissions

Anderson et al. (2007) found a positive and statistically significant association with respiratory hospital admissions, all ages, all year of 1.51% (95% CI: 0.84–2.18%) per 10 µg/m³ SO₂ that showed evidence of heterogeneity. The association remained positive and statistically significant after adjustment for some publication bias. Multicity studies gave a similar result. There were no multicity studies that examined multipollutant models, and the single-city study multipollutant results were not reviewed. A further three studies have been added to APED since (Leem et al., 1998; Jayaraman & Nidhi, 2008; Chang, Hsia & Chen, 2002), another two meeting the criteria (Wong et al., 2010a; Cakmak, Dales & Judek, 2006b) were identified in the literature search, and another one later (Chen et al., 2010b). All six found positive associations with SO₂ (two non-significant) that ranged from 0.13% to 8.2% compared with -0.5–22.5% for the previous estimates. Where there was adjustment for other pollutants (Cakmak, Dales & Judek, 2006b; Jayaraman & Nidhi, 2008; Leem et al., 1998), the estimates were reduced and remained significant in only one study (Cakmak, Dales & Judek, 2006b).

Given the chamber study findings, asthma admissions will be described here. Results for other respiratory diagnoses are described in Anderson et al. (2007). The relationship with asthma admissions was significant in children in single and multicity studies and was robust to adjustment in multipollutant models in the multicity studies (unexamined in single-city studies) (Anderson et al., 2007). Further studies published since 2006 on asthma admissions in children are also positive and statistically significant in two studies (Lee, Wong & Lau, 2006; Samoli et al., 2011a), with a range from 1.3% to 6% per 10 µg/m³ SO₂ compared with 0.8% to 9% in Anderson et al. (2007). In Samoli et al. (2011a), although control for PM₁₀ resulted in a loss of significance, it also resulted in a smaller reduction (20%) in the coefficient than when PM₁₀ was controlled for SO₂ (30% reduction). The SO₂ coefficient was stable to adjustment for NO₂ and ozone. The coefficient was said to be non-significant (direction not given) in a study in Hong Kong (Ko et al., 2007). Results in other age groups or all ages were more mixed (Anderson et al., 2007; Bell, Levy & Lin, 2008; Ko et al., 2007; Tsai et al., 2006a; Yang et al., 2007).

Anderson et al. (2007) reported a summary estimate per 10 µg/m³ SO₂ of a 2.65% (95% CI: 0.39–4.96%) increase in asthma emergency room visits in children, all year. The summary estimate was not significant in adults and the outcome was not examined in multicity studies. The database has been partially updated for emergency room visits, identifying four studies (Jalaludin et al., 2008; Ito, Thurston & Silverman, 2007; Szyszkowicz, 2008; Villeneuve et al., 2007). The latter two found no associations, but the first two found positive and statistically significant associations in children and adults,

respectively. In Jalaludin et al. (2008), the association was reduced, but remained significant, on adjustment for other pollutants; the association, however, was not robust to adjustment for NO₂ in Ito, Thurston & Silverman (2007) (only the summer association was examined). The literature search identified a few other studies of asthma emergency room visits, notably a large multicity study in Canada (Stieb et al., 2009) that found a non-significant negative association. This study was for all ages. As the Anderson meta-analysis found a greater effect in children, it would have been interesting to see the analysis split by age group. A study in Toronto did find a significant relationship in children across both sexes and in the top and bottom quintiles of socioeconomic position (Burra et al., 2009). A positive and statistically significant association was also found for SO₂ and emergency room visits for wheeze in children aged 0–2 years in a multicity study in Italy (Orazio et al., 2009).

A preliminary study from Taiwan, Province of China, used daily variations in spatially modelled pollutants as the exposure metric (Modelling may be more uncertain for SO₂ than for other pollutants, as SO₂ concentrations are characterized more by sharp peaks, which are harder to model). The study found a negative association that was not statistically significant in both single and multipollutant models for asthma emergency room visits in all age groups (Chan et al., 2009). Overall, the conclusions are unclear for SO₂ and emergency room visits for asthma, as there were mixed results in multipollutant models in the recent studies, but the larger number of earlier studies suggests the association is robust (EPA, 2008a).

Short-term exposure and cardiovascular admissions

Anderson et al. (2007) reported a summary estimate of 0.96% (95% CI: 0.13–1.79%) per 10 µg/m³ for cardiovascular admissions and 24-hour average SO₂ for all ages, all year across 5 studies and a summary estimate of 2.26% (95% CI: 1.30–3.22%) for cardiac admissions across 12 studies. A similar result was found for cardiac admissions for a multicity study in eight Italian cities and a lower one in seven European cities. The multicity studies did not include a multipollutant model and the report did not collate multipollutant model estimates for single-city studies. A further multicity study from Spain meeting the same criteria has been published since (Ballester et al., 2006) and reported an estimate of 1.33% (95% CI: 0.21–2.46%). This was not stable to adjustment for carbon monoxide, but was to other pollutants. A study in Shanghai found a positive and statistically significant association with cardiovascular admissions that was stable to adjustment for PM₁₀, but was reduced to some degree and lost statistical significance on adjustment for NO₂ (Chen et al., 2010b). The study also reported a positive and statistically significant estimate for cardiac admissions as did the study by Wong et al. (2010a). The latter two estimates were not examined in multipollutant models.

Birth outcomes

The present review concentrates on short-term exposures. Most studies of birth outcomes use longer averaging times (a month or more). Nonetheless, it should be noted that a substantial number of studies have been published in this area. A recent and thorough review concluded that SO₂ was associated with preterm birth, but not consistently with

low birth weight or small for gestational age births (Shah & Balkhair, 2011). A review by Vrijheid et al. (2011) found some evidence for an association between SO₂ and congenital cardiac anomalies. A thorough veterinary epidemiology SO₂ study in Western Canada examined whether emissions from the oil and gas industry (including SO₂) were associated with effects on the reproduction and health of beef cattle. The study showed that SO₂ exposures were not related to: abortion or stillbirth (Waldner, 2009); histopathological lesions in the immune, respiratory or nervous systems in calves that were aborted or died postnatally (Waldner & Clark, 2009); changes in lymphocyte subtype populations in blood samples from neonatal calves or yearling cattle (Bechtel, Waldner & Wickstrom, 2009a,b); or non-pregnancy, risk of disposal in pregnant cows or calving interval (Waldner & Stryhn, 2008). Gestational (but not postnatal) exposure to SO₂ above 0.9 ppb was significantly related to pathological lesions in the skeletal or cardiac muscle among calves that died (Waldner & Clark, 2009), and SO₂ exposure during the last trimester or across gestation was related to calf mortality in the first 3 months of life (Waldner, 2008). This was unexpected, given that most of the extensive, detailed end-points examined in the study did not show associations.

There are, however, studies on infant mortality that use daily average concentrations as the exposure metric. Dales et al. (2004) found an association between SO₂ and sudden infant death syndrome that was independent of adjustment for NO₂. Hajat et al. (2007) found a positive and statistically significant association between SO₂ and both neonatal and postneonatal deaths. No multipollutant modelling was performed, but there were no significant associations for other pollutants. These results were in line with earlier studies discussed by the authors, but other recent studies have found no association (Tsai et al., 2006b; Woodruff, Darrow & Parker, 2008) or a positive association that was not statistically significant (Son, Cho & Lee, 2008).

Toxicological evidence

The toxicological evidence up to about 2006/2007 has been reviewed by the EPA (2008a), although the majority of studies were pre-2004. For acute exposures and respiratory effects, it was concluded that repeated exposures to SO₂, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory and allergic responses in allergic animals. SO₂ at a concentration of 10 ppm or less failed to induce airway hyperreactivity, following a nonspecific (rather than allergic) challenge in four different animal models.

For cardiovascular effects, it was noted that, in general, vagally mediated responses in the heart have been observed at lower concentrations of SO₂ than have oxidative injuries from SO₂ metabolites in the circulation. It was not considered that the limited toxicological evidence provided biological plausibility for an effect on arrhythmias, and the evidence for effects on blood pressure and blood markers of cardiovascular risk was regarded as inconclusive.

Perturbations in potassium-, sodium- and calcium-gated channels in hippocampal or dorsal root ganglion neurons isolated from rats at 0.01–100 µM of SO₂ derivatives ex

vivo were regarded as of questionable significance, given the high doses needed for effects on the nervous system in vivo.

The evidence from animal toxicological studies was regarded as insufficient to conclude that long-term exposure to ambient SO₂ caused prolonged effects on lung morphology, lung function or decrements in lung host defence. There was evidence of oxidation and glutathione depletion in the hearts of rodents exposed by inhalation to SO₂ above 5 ppm, but this oxidative injury was not considered relevant to cardiovascular effects seen at ambient levels of SO₂.

It was concluded that toxicological studies provided very little biological plausibility for reproductive outcomes related to exposure to SO₂.

The literature search and author searches for the present review identified a number of toxicology studies on SO₂ published since 2004 that were not considered by the EPA. These studies, but not those reviewed by the EPA, are described below. None of the studies identified examined concentrations below 2 ppm, which exceeds considerably ambient concentrations, except for the veterinary epidemiology study in Canada (see section on “Birth outcomes” above).

Short-term respiratory effects

With a variety of assumptions, modelling of gas transport in theoretical airway models predicted that the local concentration of SO₂ in the upper airways of human beings would be 3–4 times higher than in rats or dogs (Tsujino, Kawakami & Kaneko, 2005). Exposure to 50 ppm SO₂ 1 hour a day for 3 days, followed by ovalbumin, exaggerated chronic allergic airway inflammation and subepithelial fibrosis (Cai et al., 2008). Another study exposed rats to 2 ppm SO₂ for 1 hour a day for 7 days prior to or without sensitization with ovalbumin. Prior exposure to SO₂ increased the mRNA and protein expression of epidermal growth factor (EGF), epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2), markers of regulation of mucus hypersecretion, and airway repair and inflammation (Li, Meng & Xie, 2008). A study that developed an animal model for chronic obstructive pulmonary disease found that 5, 10 and 20 ppm SO₂ for 3 days resulted in no change in basal mucus secretory activity in trachea preparations and a decrease (not an increase) at 40 ppm and 80 ppm. No changes were found in acetylcholine stimulated secretory activity. Single cell necrosis and loss of cilia occurred at concentrations of 10 ppm and higher (Wagner et al., 2006). SO₂ inhalation at 120 ppm for 6 hours a day for 7 days caused significant increases in the proto-oncogenes c-fos and c-jun mRNA and in protein levels in the lungs of rats (Qin & Meng, 2006a) and caused a further increase in the presence of benzo[a]pyrene. It was hypothesized that this might explain the co-carcinogenicity of SO₂ and benzo[a]pyrene in hamsters, although the EPA view was that SO₂ was not a clear co-carcinogen.

There have also been studies of lung cells in vitro. Human bronchial epithelial (BEP2D) cells were treated with a range of concentrations (0.0001–1 mM) of the SO₂ derivatives sodium bisulfite (NaHSO₃) and sodium sulfite (Na₂SO₃) in a 1:3 ratio for various

durations up to 24 hours (Li, Meng & Xie, 2007). Expression of EGF, EGFR, intercellular adhesion molecule 1 (ICAM-1) and COX-2 mRNA and protein showed a dose-dependent increase that was greatest at 30 minutes. It was suggested that this would result in mucin overproduction and inflammation, if occurring in vivo. The same dose protocol (with the addition of a 2 mM dose of the SO₂ derivatives) for 4 hours was applied to the same cell line, leading to mRNA and protein overexpression of c-fos, c-jun and c-myc at all doses, with other changes in proto-oncogenes and tumour suppressor genes at 0.1–2.0 mM (Qin & Meng, 2009).

Another study, in A549 cells, found significantly reduced cell viability in an air–liquid interface culture, with concentrations from 10 ppm to 200 ppm SO₂ (Bakand, Winder & Hayes, 2007). In the same cell line, sodium sulfite (a derivative of SO₂) at 1000–2500 µM was shown to enhance interleukin 8 (IL-8) release. IL-8 is a chemical signal involved in neutrophil recruitment and activation. IL-8 release was inhibited by a selection of asthma drugs (Yang et al., 2009). Sulfite oxidation by a mammalian peroxidase–hydrogen peroxide system, resulting in the highly reactive sulfate radical (SO₄^{•-}), has been shown for the first time in an experiment using human myeloperoxidase and human neutrophils and (bi)sulfite anions at 20–100 µM (Rangelova et al., 2012). Rangelova et al noted that healthy individuals have a mean serum concentration of 5 µM, but it can be raised in disease.

Short-term systemic and cardiovascular effects

A group from China published a series of papers on the systemic effects of SO₂. Meng & Liu, 2007, showed morphological changes in various organs in mice after inhalation of 10.6 ppm SO₂ and above for 4 hours a day for 7 days. Qin & Meng (2006b) showed a dose-related reduction in activities and mRNA levels of the detoxifying enzymes CYP2B1/2 and CYP2E1 in the lungs, and CYP2B1/2 (but not CYP2E1) in the livers of rats treated with 5.3–21.2 ppm SO₂ for 6 hours a day for 7 days. Protein oxidative damage and DNA-protein cross-links were increased in the lungs, liver and heart (in that order) in mice exposed to 5.3–21.2 ppm SO₂ for 6 hours a day for 7 days (Xie, Fan & Meng, 2007). Unsurprisingly, 21.2 ppm SO₂ for 4 hours a day for 10 days led to oxidative stress in the livers and brains of the mice. This oxidative stress was ameliorated by moderate, but not high, levels of vitamin C and by salicylic acid (Zhao H et al., 2008).

Other than the study at high doses by Xie, Fan & Meng (2007) mentioned above, no other animal studies that reported cardiovascular toxicity were picked up in the search. A review of amino acids as regulators of gaseous signalling (Li et al., 2009) notes that endogenous SO₂ (derived from cysteine) can activate guanylyl cyclase and thus elicit a variety of responses, including relaxation of vascular smooth muscle cells. A review on the same subject that is more specific to SO₂ is available (Chen S et al., 2011). In a section of the Chen et al. review, on older and newer studies of the effects of exogenous SO₂, the authors highlighted a study by Nie & Meng (2007) showing that the SO₂ derivatives NaHSO₃ and Na₂SO₃, in a 1:3 ratio at a concentration range of 5–100 µM, inhibited the sodium/calcium exchanger current in rat myocytes and that SO₂ derivative concentrations above 10 µM increased intracellular myocyte free calcium. Nie & Meng

(2007) also showed that SO₂ and its derivatives can lower blood pressure in rats. The Chen et al. review also mentioned that SO₂ and its derivatives can act as vasoconstrictors or vasodilators, depending on concentration.

The section of the Chen S et al. (2011) review on endogenous SO₂ notes that a decrease in SO₂ can protect against vascular structural remodelling in spontaneously hypertensive rats and can protect against pulmonary hypertension in rats with hypoxic pulmonary hypertension. An increase in endogenous SO₂ protected against pulmonary hypertension in monocrotaline-induced hypertension (by inhibiting smooth muscle cell proliferation), but mediated myocardial ischaemia reperfusion injury. The concentrations for these studies are not discussed in the review. The authors concluded that endogenous SO₂ is involved in regulation of cardiovascular function and that disturbances in this regulation can be found in disease.

Discussion

Although the chamber study evidence has not changed significantly, a pooled analysis of previous data suggested a tendency towards a split response between responders and non-responders that was statistically significant before (but not after) adjustment for multiple comparisons. This might suggest the need for a small increase in the safety factor.

Most of the newer toxicological evidence is at high doses, so it does not have direct implications for the guideline. The new finding of an association between gestational exposure to low levels of SO₂ and histopathological lesions in heart or skeletal muscle in beef cattle is hard to put into context, as there are no other studies of this type. It is possible that another unmeasured pollutant present at higher concentrations is actually responsible.

The review of the time-series evidence is based on studies analysed according to current practice, but it needs to be acknowledged that there are many issues that still need further discussion. As many of these issues are shared across all pollutants, they will not be discussed in detail here. These issues include statistical model choice (HEI, 2003; Erbas & Hyndman, 2005; Ito, Thurston & Silverman, 2007) and the challenges of distinguishing the effects of different pollutants in multipollutant models (Kim et al., 2007; Billionnet, Sherrill & Annesi-Maesano, 2012). The low average concentrations of SO₂, but with sharp peaks, combined with the fact that, in some studies, SO₂ is controlled for PM₁₀ that is measured only once every 6 days means that the presence of measurement error adds uncertainty to the interpretation of the multipollutant model results. More generally, exposure misclassification may be a particular issue for SO₂. Sarnat et al. (2007), in a discussion of data from four cities, concluded that ambient SO₂ was not well correlated with personal exposures to SO₂ in most subjects. It was noted that the concentrations of 24-hour average SO₂ personal exposure were very low, leading to the possibility of measurement errors in the personal exposure obscuring the relationship. In addition, the association between peak personal exposures and peak ambient concentrations may be what is of most interest. It is only necessary for these correlations

to be present in some susceptible individuals, rather than the whole population, to account for the epidemiological results.

Bearing the above points in mind, the time-series evidence continues to suggest associations with mortality that are not necessarily stable to adjustment for other pollutants. The picture for respiratory hospital admissions is similar, but asthma admissions in children seem to be more stable to adjustment for other pollutants in most cases. A robust effect on asthma admissions ties in with the chamber study evidence, although the fact that associations with asthma admissions are more variable in adults does not.

Associations are also seen with cardiovascular admissions. There are fewer studies that have tested this in multipollutant models. While there is a chamber study, a toxicology study at high doses, and a handful of panel studies on cardiovascular end-points, these recent studies on their own are insufficient to support the time-series finding one way or the other.

As the 24-hour average guideline is partly based on time-series studies, a change in the guideline might be required if none of the outcome associations were stable to adjustment for other pollutants. The present document has not reviewed multipollutant model results on single-city studies published before the Anderson et al. (2007) report. Further work would be needed to do this before coming to overall conclusions as to what outcome associations are stable to adjustment for other pollutants. Currently, the associations with asthma admissions in children seem the most robust. The Hong Kong Intervention study, where SO₂ was reduced sharply (but PM₁₀ was not) was also influential in setting the guideline, but more recent work suggests less confidence in allocating the mortality benefit to SO₂.

The 24-hour average guideline was influenced by the concentration ranges at which results had been shown in the time-series studies. These have not changed, as the lower end of the ambient concentration range was already very low in the previous studies. It is noted that this means that even quite marked changes in the size of the concentration–response function would have no effect on a guideline set on this basis. An alternative is to specify a small level of *acceptable risk* and use a concentration–response function (assuming it was robust) to derive a concentration that would minimize risk to this level. This approach should be considered as an option when it comes to the guideline revision stage.

Question C8

Are there important interactions among air pollutants in the induction of adverse health effects that should be considered in developing air quality policy?

Answer

Note. This answer does not consider interactions with host susceptibility behaviour or other factors, with the exception of temperature.

Some interactions among air pollutants change the toxicity of the mixture. These occur as physicochemical interactions in air, as well as biological interactions. In developing air quality policies, the following issues can be considered.

- There is very little evidence from health studies that the mixture of air pollutants results in significantly more health effects (synergy) than would be expected based on the information for single pollutants. However, this is largely due to a lack of data and methodological limitations.
- Very few epidemiologic studies have examined the potential of pollutants to interact. This is likely due to their moderate to high correlations. The existence of such pollutant mixtures makes it often difficult, in an uncontrolled setting, to determine either independent or synergistic effects of ambient air pollutants.
- Synergistic biological effects between ultrafine particles and transition metals and between particles and volatile organic compounds have been shown to indicate a larger combined impact on human health than would be expected from the separate entities.
- A reduction of emissions of nitrogen oxides without an accompanying abatement of volatile organic compounds may result in no change, or even in an increase of ozone concentrations close to the source.
- Airborne particles of any kind can carry aeroallergens or toxic condensed vapours, such that their impact can be substantially larger than without particles. There is a trend that the smaller the particles, the stronger the adjuvant effects. Limited evidence has been published suggesting that NO₂ can enhance allergic responses.
- In general, reduction of one component will not result in a significant increase in the health risks associated with other components. The implications for reducing PM, on (semi)volatile organic compound formation, are not evident.
- There is some evidence of interactions between pollutants and high temperature.
- Changing the air pollution mixture due to changing fuels may, under certain conditions, lead to more harmful emissions.

Rationale

Definitions of interactions

Interactions among air pollutants can be chemical, physical and biological. A chemical interaction would mean that two or more pollutants result in new components, based on the chemical composition. A well known example is nitrogen oxides and volatile organic compounds that result in the formation of ozone and other products in the presence of sunlight. In physical interactions, solid particles act as absorbers for organic compounds, affecting their transport through air and in the respiratory tract. Biologically, interactions are distinguished by the mode of action: dose addition (similar action), effect or response addition (dissimilar action), and complex interactions (synergistic, potentiating and antagonistic). Dose addition means that the chemicals in the mixture do not affect the toxicity of one another and that each component has different effects – for example, one component with produce lung inflammation, whereas a second component causes rhinitis only. Each of the chemicals in the mixture contributes to the toxicity of the mixture in proportion to its dose. In the case of response or effect addition, the components in a mixture have the same toxicological profile – for example, all lead to inflammation in the lung. Response addition is determined by summing the responses of each toxicant in a mixture.

For interactions, compounds may interact with one another, modifying the magnitude and sometimes the nature of the toxic effect. This modification may make the composite effect stronger or weaker. An interaction might occur in the toxicokinetic phase (processes of uptake, distribution, metabolism and excretion) or in the toxicodynamic phase (effects of chemicals on the receptor, cellular target or organ). In the case of interaction, one cannot predict the toxicity based on exposure concentrations, and dose-response relationships are required to assess whether or not, for example, stronger responses occur than would be expected based on each of the pollutants alone.

Atmospheric chemistry

Reducing tailpipe soot may lead in specific cases to an increase NO₂ and ultrafine particles

Reducing the emission of soot particles from motor vehicles has in some cases significantly altered the chemical composition and particle size distributions in specific urban environments (Keuken et al., 2012; Herner et al., 2011). When filter traps were applied without catalysts (urea selective catalytic reduction), NO₂ concentrations increased locally at traffic sites, even though a total reduction in concentrations of nitrogen oxides was observed. The regulatory relevance of this shift is clear, although the real health impact of this change in the emission is still under discussion (Keuken et al., 2012). In these specific cases, mass-related emission of PM was significantly reduced with the change of the combustion conditions and the use of a particle filter without urea selective catalytic reduction. The use of particle traps significantly removed the larger particles and, hence, led to formation of a nucleation mode with a significantly increased particle number concentration of about 10 nm at end of the tailpipe (Herner et al., 2011),

and a shift of the mode led to a particle number concentration of about 10–30 nm at some distance –for example, that of a pedestrian on a street (Harrison, Beddows & Dall’Osto, 2011; Casati et al., 2007).

Changing reactivity over time or with increasing distance from the source

Particle reactivity is believed to be an important characteristic with direct influence on the hazard potential. Particle reactivity is a general term that includes, for example, the particle intrinsic formation potential of reactive oxygen species and the ability to catalyse redox reactions. Its possible importance for health is currently being discussed (Shiraiwa, Selzle & Pöschl, 2012). Initial studies on spatial and temporal variations of particle reactivity parameters have been conducted (Boogaard et al., 2012a; Künzli et al., 2006). Still missing is the link between particle reactivity and other particle characteristics, the actual mechanisms triggered, and the ageing and/or changes of particle reactivity during atmospheric transport due to chemical reactions. Understanding how particle surface properties are altered during atmospheric transport, physically and chemically, may be one key in linking particle characteristics and emissions to health effects.

Secondary organic aerosol

Although laboratory experiments have shown that organic compounds in both gasoline fuel and diesel engine exhaust can form secondary organic aerosols, the fractional contribution from gasoline and diesel exhaust emissions to ambient secondary organic aerosols in urban environments is poorly understood. Recently, Bahreini et al. (2012) demonstrated that, in Los Angeles, the contribution from diesel emissions to secondary organic aerosol formation is very low and that gasoline emissions dominate diesel exhaust emissions in forming secondary organic aerosol mass. Chamber studies performed in Europe seem to confirm this hypothesis. In a very recent paper, Gentner et al. (2012) reported that diesel exhaust is seven times more efficient at forming aerosol than gasoline exhaust, that both sources are important for air quality and, depending on a region’s fuel use, that diesel is responsible for 65–90% of the vehicle-derived secondary organic aerosols. These conflicting results have important implications for air quality policy, but at present large uncertainties exist.

Verma et al. (2009b) have shown for Los Angeles in summer that both primary and secondary particles possess high redox activity; however, photochemical transformations of primary emissions with atmospheric ageing enhance the toxicological potency of primary particles, by generating oxidative stress and leading to subsequent cell damage.

Studies by Biswas et al. (2009) – using direct exhaust PM emissions from heavy duty vehicles, with and without emission abatement technologies implemented – suggest that the semivolatile fraction of particles are far more oxidative than solid (carbon) particles. It is also possible, in our opinion, that the secondary organic aerosols formed from the condensation of previously volatilized PM are highly oxidative.

Ozone and organics

Reactions of ozone with certain organic molecules that occur indoors at certain concentrations can produce short-lived products that are highly irritating, relative to the reaction precursors, and may also have long-term health effects. Known products of indoor ozone reactions include such compounds as formaldehyde, acetaldehyde and other organic acids. Some of these compounds are known to cause ill health in human beings (Weschler, 2006). The EPA Building Assessment Survey and Evaluation study data was analysed for associations between ambient ozone concentrations and building-related symptom prevalence (Apte, Buchanan & Mendell, 2008). Ambient ozone correlated with indoor concentrations of some aldehydes, a pattern suggesting the occurrence of indoor ozone chemistry. Apte, Buchanan & Mendell (2008) hypothesized that ozone-initiated indoor reactions play an important role in indoor air quality and building occupant health. They also hypothesized that ozone carried along into buildings from the outdoor air is involved in increasing the frequency and the range of upper and lower respiratory, mucosal, and neurological symptoms by as much as a factor of 2 when ambient ozone levels increase from those found in low-ozone regions to those typical of high-ozone regions.

Secondary inorganic aerosols

In regions with high photochemical activity, the reduction of PM mass pollution and the possible increase in frequency of droughts may lead to an increase in midday nucleation episodes with a consequent increase in levels of secondary nano-size or ultrafine particles. Thus, in highly polluted atmospheres, the secondary PM mass grows by condensation on pre-existent particles; however, in cleaner conditions, and especially under high insolation and low relative humidity, new formation on nanoparticles (nucleation) from gaseous precursors may dominate the condensation sink in urban areas (Reche et al., 2011). The nucleation starts from the oxidation of SO₂ and the subsequent interaction with ammonia, and these nanoparticles immediately grow – probably by condensation of volatile organic compounds on the nucleated particles (Kulmala & Kerminen, 2008).

Another key atmospheric component is urban ammonia. This is emitted mostly by traffic and other fugitive sources, such as city waste containers and sewage, and is also emitted from animal farming. Ammonia is an alkaline gas and, when emitted in a high NO₂ scenario, may enhance the formation of ammonium nitrate (a major component of PM_{2.5}). Furthermore, the levels of ammonium nitrate may also increase due to the marked decrease of SO₂ emissions that yielded a marked decrease of ammonium sulfate levels across Europe. This is expected to occur because sulfuric acid is more reactive with ammonia, and most of ammonia is consumed by sulfuric acid; when sulfuric acid decreases and more ammonia is available, more ammonium nitrate can be formed from nitric acid and ammonia.

Inorganic aerosols and metals

Thus, pure ammonium sulfate particles are rare in the atmosphere, and they usually occur as a coating on (or are coated by) other substances. They can be formed from SO₂ emissions being converted photochemically into sulfuric acid. This acid coats the outside of other particles, such as metal oxide particles, which can come from the same power plant, from brake wear of cars and trucks, from metal processing, and so on. Alternatively, they may adsorb metal particles on their surface. By internal mixing, the surface components diffuse towards the core of the particle, leading to reactions between acidic sulfates and metals, converting insoluble (and hence weakly toxic) metal oxides into soluble metals. This is critical because transition metals can catalytically induce the production of highly reactive oxygenating compounds in the lung and elsewhere in the body. For example, Ghio et al. (1999) reported that soluble iron concentrations correlate with sulfate concentrations in particle filters and that the ability of soluble extracts from the particles to generate damaging oxidants is directly proportional to the sulfate concentrations. More recently, Rubasinghege et al. (2010) simulated the transformation of non-bioavailable iron to dissolved and (hence) bioavailable iron in atmospheric iron particles in the presence of acids, in both light and dark conditions. The presence of sulfuric acid on the particles results in a dramatic increase in the bioavailable iron.

Metals are not the only case where the presence of sulfates can change the toxicity of other particle components. Popovicheva et al. (2011) showed that the extent of water uptake and modification of elemental carbon particles depended on the sulfate content of the particles. Also, Li W et al. (2011) reported that sulfate aided the ageing of freshly emitted soot particles, which occurred within 200–400 m of major roads.

Wu et al. (2007) examined the effect of ammonium sulfate aerosol on the photochemical reactions of toluene (mostly from cars) and nitrogen oxides to form secondary organic particles. They found that the sulfate particles reduced the time to reach maximum concentrations of secondary organic aerosols, and also increased the total aerosol yield from toluene. That is, in the presence of sulfates, more gaseous emissions from mobile sources will be converted into particles.

Ozone and NO₂

It is clear that ozone precursors make an important hemispheric (external to the EU) contribution, but because the high ozone levels are recorded mostly in rural areas, policy pressure on PM and nitrogen oxides is much higher than on ozone. The way of abating ozone levels by local measures that focus on local ozone precursors is very complex. This is because the relationship between ozone and volatile organic compounds and between ozone and NO₂ is not linear, so that specific cases of reducing NO₂ without compensating for the decrease of volatile organic compounds, or vice versa, may result in ineffective results, or even in an increase in ozone. On the other hand, biogenic volatile organic compounds may also be involved in the process. It is expected, however, that measures applied to reducing nitrogen oxides and industrial volatile organic compounds and also climate measures to abate methane (an ozone precursor) may contribute to abating

ambient ozone. But it is also true that it is very difficult to quantify the impact of such abatement.

Interaction due to ultraviolet and/or changes in volatile organic compound and/or particulate organic carbon composition

It is well known that photochemical reactions by, for example, ultraviolet and visible radiation have a significant impact on the gaseous and particulate chemical composition of the atmosphere. One of the components currently believed to be relevant to health is organic carbon, either in the gas phase or the particulate phase. Jimenez et al. (2009) present an overview of the evolution of organic aerosols in the atmosphere. Studies closer to the source – for example, investigations of the photo-oxidation of organic compounds from motor vehicle emissions – also show significant changes (Miracolo et al., 2010). Any changes in the composition of organic carbon compounds in the atmosphere are of great importance, since their relevance to health (independent of gaseous or particle phase) has a huge spectrum, from no health effects to high toxicity. To understand the changes on a small scales – for example, near sources and close to the public – as well as the changes occurring during transport, they have to be monitored more closely.

Toxicology

Already a decade ago, Stone et al. concluded that there was evidence that synergistic interactions occur between ultrafine particles and transition metals, between particles and allergens, and between particles and volatile organic compounds, such that reductions of concentrations of one component will lead to less health effects related to the other (Stone et al., 2003). Participants at a 2007 meeting on combustion by-products (Dellinger et al., 2008) concluded that metals contained in combustion-generated airborne particles mediate the formation of toxic air pollutants, such as polychlorinated dibenzo-*p*-dioxins and dibenzofurans and persistent free radicals associated with oxidative stress, inflammation and other toxic effects.

PM components and ozone

Some evidence suggests that ambient concentrations of ozone can increase the biological potency of particles. Ozonized diesel exhaust particles may play a role in inducing lung responses to ambient PM (Madden et al., 2000). Similar findings have been observed in clinical studies (Bosson et al., 2008). In terms of vascular and cardiac impairment in rats inhaling ozone and diesel exhaust particles, Kodavanti et al. (2011) reported that the joint effect of exposure to ozone (0.803 mg/m³) and diesel exhaust particles (2.2 mg/m³) was less prominent than exposure to either substance alone. An explanation for this might be found in the duration of the exposure protocol (1 day a week for 16 weeks) that may have led to adaptive responses known to occur for ozone. Also, concentrations as low as 0.423 mg/m³ ozone increased the toxic response of mixtures of carbon and ammonium sulfate particles in rats – including histopathological markers of lung injury, bronchoalveolar lung fluid proteins, and measures of the function of the lung's innate immunological defences – whereas these effects were not observed with ozone alone (Kleinman et al., 2003).

PM components and nitrogen oxides

As NO₂ can cause nitrative stress (and production of nitric oxide via nitrite) and PM can cause oxidative stress (and production of superoxide radicals), the combination of exposure to both might increase production of peroxyxynitrite over and above either pollutant alone. Peroxyxynitrite is recognized as a key intermediate, with the potential to affect protein function (Gunaydin & Houk, 2009). It is formed from the reaction of nitric oxide and the superoxide radical. NO₂, as is well known, can lead to increased levels of circulating nitrite and nitrate. Nitrite can be reduced back to nitric oxide and the NO₂ radical in remote tissues (Lundberg, Weitzberg & Gladwin, 2008). Overall, co-exposure to PM and NO₂ may lead to simple additive effects in the lung, and reduction of either one of these components may therefore lead to lower effect estimates in epidemiological studies of the other component. Although the literature on this is very sparse, it seems unlikely that the reduction of PM has a major effect on the health impacts of nitrogen oxides.

PM and other gases and/or vapours

Some papers show that the oxidative potential and toxicity of soot decreases up to 75% after heating and losing the external organic carbon shell (Biswas et al., 2009). Also, volatile organic compounds are able to form PM (Robinson et al., 2007; Jimenez et al., 2009). In addition, studies of human beings and diesel engine exhaust and clean carbon particles (Mills et al., 2011) strongly suggest that organic chemical compounds on the surface of the carbon particles are responsible for immediate cardiovascular responses. Interestingly, reducing the amount of soot can lead to an increase in NO₂, but the net effect is still reduced adverse effects on health (Lucking et al., 2011).

PM: carbon and iron

Animals exposed to soot particles at a concentration of 250 µg/m³ and to iron alone at a concentration of 57 µg/m³ had no adverse respiratory effects, but a synergistic interaction between soot and iron particles, in the combined exposure, was identified with strong inflammatory responses (Zhou et al., 2003).

Ozone and nitrogen oxides

Very little is known about the effects of co-exposures of ozone and NO₂. Decades ago, Mautz et al. (1988) were able to show synergistic toxic responses in mice exposed to these pollutants. Since ozone and NO₂ will form nitric acid vapour and nitrate radicals, the synergistic effects were explained by chemical interactions (Mautz et al., 1988). Various chemical compounds, as well as allergenic proteins, are efficiently oxygenated and nitrated upon exposure to ozone and NO₂, which leads to an enhancement of their toxicity and allergenicity (Shiraiwa, Selzle & Pöschl, 2012). Oxidative stress has been postulated as the underlying mechanism for adverse health outcomes, suggesting a rather unifying and standard response.

Interactions with aeroallergens

The implications of co-exposures to air pollutants and aeroallergens are a rather complex issue, with both antagonistic and synergistic effects observed, depending on the sequence and levels of exposures. Eggleston (2009) concluded that “the same environmental exposures that may cause increased symptoms at one point in time may be protective when the exposure occurs earlier or at high enough levels”.

PM. Co-exposures to aeroallergens (such as grass pollen) and particles result in synergistic effects that lead to much stronger allergic responses in experimental animals and human beings than the sum of the responses to each of these constituents (D’Amato et al., 2005; Steerenberg et al., 2003; Diaz-Sanchez et al., 1999). However, this is different from studies in which the effects of particles have been studied on already allergic subjects. For example, controlled exposures, lasting 2 hours with intermittent exercise, to diluted diesel engine exhaust at a particle mass concentration of $100 \mu\text{g}/\text{m}^3$ did not evoke clear and consistent lower-airway or systemic immunological or inflammatory responses in mildly asthmatic subjects, with or without accompanying challenge with cat allergen (Riedl et al., 2012). Likewise, these diesel engine exhaust exposures did not significantly increase nonspecific or allergen-specific bronchial reactivity. A few isolated statistically significant or near-significant changes were observed during and after exposure to diesel engine exhaust, including increases in nonspecific symptoms (such as headache and nausea) suggestive of subtle, rapid-onset systemic effects. From several inhalation studies with $\text{PM}_{2.5}$ in rat and mice models for allergic asthma, it was concluded that allergic inflammation and other effects can be enhanced by PM exposures for all size ranges of PM_{10} (Kleinman et al., 2007; Li N et al., 2010; Heidenfelder et al., 2009). However, such an interaction points more towards an enhancement of an existing disease and not to a synergy due to co-exposures.

In summary, ambient particles can, indeed, act as a carrier and adjuvant of aeroallergens, and reductions of PM may therefore result in stronger effects than those based on the concentration–response functions of PM alone, depending on the nature of the co-exposures.

NO_2 . Alberg et al (2011) were not able to detect an impact of NO_2 on allergy induced by ovalbumin, whereas diesel exhaust particles were shown to be a potent adjuvant. In contrast, Bevelander et al. (2007) and Hodgkins et al. (2010) did find a potentiating effect of NO_2 within the concentration range used by Alberg et al. (2011) (5–25 ppm) when NO_2 exposure occurred immediately beforehand and ovalbumin exposure was by inhalation. Recent *in vitro* findings suggested that levels of SO_2 and NO_2 below current EU health based exposure standards can exacerbate pollen allergy on susceptible subjects (Sousa et al., 2012). Moreover, exposure to NO_2 significantly enhanced lung inflammation and airway reactivity in animals that were treated with ovalbumin (Layachi et al., 2012). So, there are mixed results in human clinical studies in which NO_2 exposure preceded allergen exposure.

Changing fuel composition

There is conflicting evidence about the extent to which biodiesel exhaust emissions present a lower risk to human health when compared with petroleum diesel emissions (Swanson, Madden & Ghio, 2007). German studies have shown significantly increased mutagenic effects, by a factor of 10, of particle extracts from rapeseed oil in comparison with fossil diesel fuel; and the gaseous phase caused even stronger mutagenicity (Bünger et al., 2007). Biodiesel (rapeseed oil methyl ester) has been shown to have a four times higher cytotoxicity than conventional fossil diesel under idling conditions, while no differences were observed for the transient state (Bünger et al., 2000). This was particularly evident for mixtures of rapeseed and fossil diesel, suggesting that a mixture can lead to more harmful particulate emissions. So far, the opposite was found by others: no differences for cytotoxicity with vehicle emissions under idling conditions (Jalava et al., 2010).

Results indicate an elevated mortality risk from short-term exposure to ultrafine particles, highlighting the potential importance of locally produced particles. In an epidemiological study in Erfurt, Germany, decreases in RRs for short-term associations of air pollution were calculated as pollution concentrations decreased and control measures were implemented. However, the mass concentration changes did not explain the variation in the coefficients for NO₂, carbon monoxide, ultrafine particles, and ozone (Breitner et al., 2009). The control measures included restructuring of the eastern bloc industries, a changed car fleet (the number of cars with catalytic converters increased over time, as did the number of cars in general) and complete fuel replacement and an exchange from brown coal to natural gas in power plants and in domestic heating (Acker et al., 1998).

Epidemiology

For epidemiological studies, we define a statistical interaction among air pollutants as a case where the exposure to the two pollutants generates an effect that is greater than that observed for either individual pollutant. Generally speaking, epidemiological studies have not extensively examined the potential for statistical interactions among pollutants. This is likely due to the moderate to high correlation among pollutants and the existence of pollutant mixtures, making it often difficult, in a uncontrolled setting, to determine either independent or synergistic effects of ambient air pollutants.

Of the few studies to date that have been undertaken, there is very limited evidence of an interaction among pollutants, and most studies that have tested for interactions have not observed any. For example, in a cohort of 2460 subjects recruited from a pulmonary clinic, researchers analysed the association between chronic exposure to air pollution and the prevalence of ischaemic heart disease (Beckerman et al., 2012). While effects from NO₂ were observed, there was no evidence of interactions between it and either ozone or PM_{2.5}. Coogan et al. (2012) examined the association between air pollution and incidence of hypertension and diabetes mellitus in African-American women living in Los Angeles. Again, an effect of NO₂ was observed, but there was no evidence of an interaction with PM_{2.5}. In contrast, a study of infant mortality in Mexico City observed that its association with PM₁₀ was heightened when high concentrations of ozone were also present

(Carbajal-Arroyo et al., 2011). Finally, in a study of 29 European cities, Katsouyanni et al. (2001) reported that cities with higher long-term average NO₂ demonstrated a greater effect of daily PM₁₀ on mortality than did cities with low average NO₂. Rather than demonstrating an interaction of pollutants, per se, this observation likely represents a greater contribution of traffic to PM₁₀ in the cities with high levels of NO₂.

Several studies have examined whether air pollutants modify or interact with the effects of temperature. Most researchers have focused on PM and ozone, since these pollutants are associated with mortality and are often correlated with higher temperatures. The results to date are mixed, as some investigators reported air pollutants modified the temperature effect, while others reported no interactions, but rather independent effects of pollution and temperature. For example, ozone and temperature were reported to interact during the 2003 heat wave in nine French cities and in 100 cities studied over several summers in the United States (Ren et al., 2008a; Filleul et al., 2006b). In addition, in a new study of nine European cities (Analitis et al., 2013) from the EuroHEAT project, there is evidence that supports interactive effects between heat waves and high ozone and PM₁₀ concentrations. This interaction was more evident and significant in the northern cities, rather than in the Mediterranean ones. In contrast, no interaction between temperature and ozone was reported for cities in Italy and for Toronto, Canada, and only modest evidence for an interaction was observed in a multicity study in Italy (Stafoggia et al., 2008; Rainham & Smoyer-Tomic, 2003). In addition, studies in cities in the United States that examined temperature plus PM_{2.5}, PM₁₀, ozone and NO₂ failed to find any interaction (Basu, Feng & Ostro, 2008; Zanobetti & Schwartz, 2008; Ostro, Rauch & Green, 2011).

Finally, a few epidemiological studies considered the impact of exposure to both air pollution and aeroallergens. For example, Anderson et al. (1998) examined the interactive effects of air pollutants and pollen on hospital admissions for asthma in London. While effects were observed for several air pollutants, there was no evidence that exposure to pollen exacerbated the effect of air pollution.

In summary, for policy consideration, based on the limited number of studies that have examined this issue, there is mixed evidence of potential interactions among pollutants or pollution and temperature. The one potential exception may be that related to traffic, where the different mixtures of various pollutants may have a varied impact on the magnitude of the effect on health under investigation. However, it is very difficult in these epidemiological studies to separate the independent effect of individual pollutants in the mixture and thereby determine whether an interaction exists.

Questions A7 & C9

Are there critical data gaps to be filled to help answer A, B and C questions more fully in the future?

Answer

For most air pollutants covered under the REVIHAAP project, several critical data gaps have been identified that prevent a comprehensive and thorough assessment of health hazards and concentration–response functions. More epidemiological studies that contribute to updated exposure–response functions based on meta-analyses for integrated risk assessments will result in a significant reduction in the outstanding uncertainties in risk quantification for the hazards currently identified. The coordinated application of atmospheric science, epidemiological, controlled human exposure and toxicological studies is needed to advance our understanding of the sources responsible for the most harmful emissions, physical–chemical composition of the pollution and biological mechanisms that lead to adverse effects on health. Such studies should include better characterization of the pollution mix, improved exposure assessments and better identification of susceptible groups in the general population. The correlation between many regulated air pollutants is often high, and large uncertainties exist about the effects on human health of short- and long-term exposures to non-regulated components of the air pollution mix, including some size fractions and metrics of PM. The currently regulated pollutants PM, NO₂ and ozone, as well as such important particle metrics as black carbon and coarse and ultrafine particles, often have been assessed independently; this is a critical gap. Furthermore, the REVIHAAP review has clearly identified traffic as one of the major air pollution sources that affect health in Europe; however, it remains uncertain whether reducing concentrations of currently regulated pollutants will directly lead to a decrease in the health impacts of traffic-related air pollution.

Air pollution should therefore be considered to be one complex mix, and conditions under which this mix has the largest effect on human health need to be identified. In addition to (or even instead of) studies on single components or metrics, the *one-atmosphere* concept has been put forward as a novel way to investigate the effects on health of complex mixes. Advances in atmospheric modelling, in conjunction with validation studies that use targeted monitoring campaigns, will provide a more efficient way forward in research on health effects, rather than relying on increasing the number of components measured by routine monitoring networks.

Rationale

The information and data identified in the following text would have allowed us to answer more fully the other questions in sections A–C. Even though some of the text is pollutant-specific, we recommend a comprehensive approach to studying pollutant mixes and to conducting complementary atmospheric science, epidemiological, controlled

human exposure and toxicological studies that allow assessment of all causal chains that link pollution emissions to effects on health.

General issues

The following general issues are of relevance when addressing critical data gaps.

- The amount of literature on the adverse effects on health of air pollution is very large, making its thorough evaluation time consuming. Given the need for a systematic evaluation of various types of evidence, consideration should be given to the development or expansion of resources, to enable regular critical, systematic and quantitative evaluation of the recent literature in relation to science-policy issues of particular relevance to Europe.
- Future studies should consider air pollution as a complex mix, and conditions need to be identified under which this mix has the largest effect on human health. A novel way to investigate the health effects of complex mixes is the one-atmosphere concept.
- There is a clear need for more evaluation of the usefulness of two-pollutant and/or multipollutant statistical models in epidemiological studies when pollutants are highly correlated.
- Collaboration is needed between the health and atmospheric sciences, for both complex monitoring and modelling, especially for exposure to complex pollutant mixes with strong spatial and temporal variability.
- In coordination with health specialists, more monitoring is needed, both in a regular way and in projects. The use of supersites to perform simultaneous studies with a multipollutant approach that uses the same monitoring and health evaluation approaches across Europe is highly recommended.
- Further research is needed on the use of health evidence for risk assessment and policy analysis. More specifically, it is needed on: (a) cause-specific PM exposure–response function shape, with a focus on non-linearities at both the high and low ends; (b) the characterization of uncertainty therein and, more broadly; (c) cost–benefit assessment and cost–effectiveness analysis, with recommendations, for example, for further work on the uncertainties in the exposure estimates from the GAINS model, which could be included in a unified estimate of uncertainty due to the major inputs for risk estimates.

PM

1. Health outcomes

This area includes: novel health outcomes; exposure– (concentration–)response functions; chemical composition and sources; distance from major roads; and the health benefits of reducing PM.

- **Novel health outcomes.** The literature on the long-term effects of exposure to PM_{2.5} suggests additional systemic health effects beyond the respiratory and cardiovascular

systems – for example, effects on the central nervous system, the progression of Alzheimer’s and Parkinson’s diseases, developmental outcomes in children, and such reproductive health outcomes as low birth weight (Questions A1 and A2). These other health effects are not yet being considered for health impact assessment, because of a lack of sufficient evidence. For this reason, more information on the underlying biological mechanisms should be generated to support a potential causal – that is, explanatory – pathway for these effects.

- **Exposure– (concentration–)response functions.** Since additional PM exposure metrics (other than PM_{10} and $PM_{2.5}$), such as ultrafine particle number concentration, black carbon or oxidative potential, have been reported, concentration–response functions need to be established for these parameters and for newly identified health outcomes (Questions A2–A6). This will also require the generation of large data sets on these exposure metrics.
- **Chemical composition and sources.** Although knowledge of the roles of chemical composition and emission sources of particles is accumulating, work to date gives no clear picture of which of these predict the highest hazard within the PM mixture (Question A2). Toxicological and controlled human exposure studies are expected to provide the basic understanding necessary to resolve this critical issue and to open opportunities for developing target reduction strategies. This would require confirmation by real world epidemiological studies based on sufficient chemical composition and source-related exposure data.
- **Distance from major roads.** A thorough evaluation of the long-term effects of living near major roads is needed to determine which specific pollutants (including elemental carbon, organic carbon, trace metals, non-tailpipe emissions and NO_2) or mixes of them may be responsible and whether the toxicity of pollutants is different near or further away from roads (Question C1). This may include reanalyses of existing epidemiological studies, looking at the relationship between living near roads and specific air pollutants. Improvements in land use regression models would allow a more detailed insight into the spatial variability in health effects associated with various sources of pollutants. This can be used for planning activities – for example, in urban areas.
- **Health benefits of reducing PM.** Although very few studies have concluded that strategies for reducing PM may not lead to improved health associated with other pollutants (Question D2), investigations of the implications of interactions among components in the air pollution mix and of the influence of abatement strategies on risk estimates are mostly lacking (Question C8).

2. PM characteristics

A number of PM size fractions and components were identified as relevant to future air quality policy. In many instances however, evidence was missing on health effects, especially those associated with long-term exposures. Comparisons of the hazardousness of the components and an adjustment of their individual effects due to other components

have rarely been studied, and (for some components) the spatial heterogeneity provides a challenge. Of special interest are the following pollutants.

- **Coarse particles (PM_{2.5-10}).** Several studies available to date have provided evidence for associations between short-term exposures to coarse particles and health. Data from clinical studies are scarce; and toxicological studies report that coarse particles can be equally as toxic as PM_{2.5} on a mass basis. Studies that assess the long-term health effects of coarse particles and studies that indicate the relative importance of the various sources of coarse particles – including road dust, desert dust, construction dust and volcanic ash, among others– are lacking (Question A2). Also, data that help to reduce exposure misclassification are needed, since such misclassification could obscure exposure–response relationships for coarse particles.
- **Ultrafine particles.** Critical data gaps include: (a) lack of epidemiological evidence on the effect of ultrafine particles on health, with only a handful of studies published on this topic; (b) insufficient understanding of whether the effects of ultrafine particles are independent of those of PM_{2.5} and PM₁₀; and (c) evidence of which ultrafine particle physical or chemical characteristics are most significant to health. There is a lack of data on the effects of short-term exposures to ultrafine particles, and there are no epidemiological studies of long-term exposure to ultrafine particles (Question A2).
- **Carbonaceous particles, including black carbon or elemental carbon, and primary and secondary organic aerosols.** This gap in evidence is underscored by soot and elemental carbon having been identified as carriers of toxic (semi-)volatile compounds (Questions A2 and C8). The role of organic particles is not well understood, and data are needed on the role of the toxicity of primary or secondary organic aerosols.
- **Particles from different sources and the use of source apportionment tools in epidemiological studies.** The main questions about the differences in the health effects of particles originating from different emission sources, including both natural and anthropogenic ones, is the relative contribution of these source-associated particles in comparison with the rest of the pollution mix. Since exposure to particles can also be from indoor sources or other routes of exposures (such as consumer products), the combined effects should be assessed, including possible interactions. As controls for exhaust emissions become more widespread, emissions from non-combustion sources will make up a larger proportion of vehicle emissions. Although traffic-related non-combustion PM emissions are not regulated in the same way as exhaust emissions are, they will need to be considered more closely in future assessments of the effect of motor vehicles on human health (Questions A2 and C1). Furthermore, a category of PM, which is poorly studied in the general environment, is bioaerosols, such as virus particles, bacteria, fungal spores and plant pollen. Primary biological aerosols can range in size from 10 nm (small virus particles) to 100 µm (pollen grains), and some have been associated with infectious diseases, such as Q fever.

- **Secondary inorganic aerosols.** The toxicological hazard of secondary inorganic aerosols is classified as relatively low. Yet, epidemiological studies continue to report associations between sulfate or nitrate and human health. It has been suggested that associated metals or adsorbed components, such as organics, play a significant role in these observations or that they represent a mix of certain sources. Specifically, data are lacking on causal constituents or associated toxins that can explain the strong association between sulfates and adverse effects on health (Question A2). Atmospheric chemistry might be able to provide some insights about the morphology and composition of PM.

3. Exposure assessment and monitoring

Time-resolved measures of size fractions, as well as the chemical components of PM, are major gaps in exposure (including personal) studies. Specific gaps include the following.

- **Exposure monitoring.** There is a need to better assess how – that is, where, how much and when – people are exposed to health relevant pollutants and, subsequently, to: (a) identify key pollutants; (b) measure and model, with appropriate instruments, the most relevant temporal and spatial resolution; (c) measure and model not only ambient concentrations, but also those in microenvironments; (d) carry out measurements of personal exposure; and (e) collect data on population time-activity patterns (Questions A3 and C10).
- **Monitoring sites.** Larger and more specific studies that simultaneously cover a number of cities, regions and long study periods are needed to yield powerful results. The creation of so-called supersites or special sites should be considered, but mobile measurement units may also be employed to complement fixed site measurements in specific situations, designed in collaboration with health researchers. Additional air quality parameters and new instrumentation data – for example, from size-segregated ultrafine particles, online PM speciation measurements with aerosol mass spectrometers or other online PM speciation instruments – and surface area or bioreactivity measurements should be considered. The use of satellite-based estimates should also be increased (Question A2).
- **Modelling.** The use of modelling approaches for spatio-temporal variations should be enhanced. Experimental data should also be used to validate models – for example, dispersion models or models using satellite-based or remote sensing data. More needs to be done on improving modelling and on developing low-cost and reliable methods of personal monitoring. The high spatial variability of pollutants, such as coarse PM, should be captured by advances in modelling such pollutants.
- **Internal doses, deposition patterns and distribution for various size fractions of PM.** Insight into the dose delivered and the rate of delivery would facilitate the use of in vitro data for risk assessment and reduce uncertainties about extrapolation from in vivo studies to human health. Insight into the relationship between external concentration, exposure, distribution and internal dose would contribute to the

evidence on the effects of long-term exposure and would provide evidence to support such novel adverse effects as those on the central nervous system (Question A2).

- **Characterization of exposure to road traffic.** Improved techniques on exposure assessment related to traffic are needed; specifically ones that can help discriminate between engine exhaust and non-exhaust traffic-derived emissions (Questions A2 and C1).

Ozone

For ozone, there is a need to better understand: long-term effects; burden of disease estimates; indoor ozone; the effectiveness of abatement measures; threshold levels; and the mechanisms behind its effects on birth outcomes.

- **Long-term effects.** There is a need to better understand the long-term effects (mortality effects and also morbidity effects related to the respiratory system and other systems) of ozone. There are very few studies of long-term exposure to ozone with meaningful spatial contrasts in ozone concentrations, without correlated covariates. Given that ozone is a powerful oxidant against which the body is protected to some degree by endogenous antioxidants, a better alignment of toxicological and epidemiological studies, with emphasis on long-term exposure, is needed (Question B1).
- **Burden of disease estimates.** The evidence base used in the CAFE Programme to estimate the burden of disease due to the effects of ozone (such as years of life lost due to ozone mortality) should be reassessed (Questions B1–B3).
- **Indoor ozone.** There is a body of evidence on short-term health effects of ozone indoors due to infiltration from outdoors (Question B4). It seems that indoor reactions in which infiltrating outdoor ozone is involved produce by-products that may affect human health. More studies are needed to support this evidence.
- **Effectiveness of ozone abatement measures.** Since important adverse effects on health have been observed, a need has emerged to evaluate the effectiveness of measures for ozone abatement and to increase the understanding of mechanisms that lead to ozone formation related to changes in emission patterns. Regional versus hemispheric ozone origins need more investigation. Studies on the presence or absence of a threshold for ozone effects are strongly recommended (Question B2). If there is a threshold, tackling the peaks in regional ozone is likely to be the most effective policy. If there is no threshold, reducing the hemispheric background becomes a major imperative.
- **Threshold levels.** Since no clear threshold level is established for either short-term or long-term effects, the estimated total burden of disease associated with ozone depends very much on the cut-off value selected. Different cut-off values (with combinations of concentration and season) can result in large differences in burden of disease estimates.

- **Mechanisms behind ozone effects on birth outcomes.** Some recent studies have reported associations between first trimester ozone and birth outcomes – in particular, preterm birth. Ozone is a potent oxidant known to cause inflammation, and this has been suggested as a possible mechanism behind its effects. Maternal vitamin D levels are important for fetal health, and vitamin D deficiency during pregnancy has been associated with circulating inflammatory proteins and pre-eclampsia. Also, inflammation in early pregnancy is associated with an increased risk of preterm delivery, and the effect of first trimester ozone on risk of preterm birth is larger among asthmatic mothers. More evidence on these novel outcomes is needed.

NO₂

This section covers data gaps in relation to: toxicological and controlled human exposure studies; exposure assessment and monitoring; and epidemiological studies.

1. Toxicological and controlled human exposure studies

- **Direct effects of NO₂ or NO₂ as a representative substance of air pollution from road traffic.** It is needed to verify whether it is plausible that NO₂ exerts a direct effect on human health at current European ambient levels or whether it simply acts as a representative of other harmful components of the mix that also includes ultrafine particles and other pollutants (Questions C2 and C8). Such data are particularly relevant in areas where NO₂ levels are rising while PM levels are decreasing, due to effective emission control strategies. At present, it is not known how this would affect the toxicity of the total air pollution mix and how this would change the (slope of the) concentration–response relationships for NO₂.
- **Mechanisms of action.** Studies are needed that not only identify biological mechanisms that lead to clinical symptoms and disease, but that also examine whether the mechanisms apply across all concentrations, or only above a certain concentration or threshold level that can be identified for NO₂ as a component of a complex mix (Question C2). This data gap would include systemic nitrate stress and effects on the cardiovascular and central nervous systems, as current guidelines do not consider these types of effects, due to a lack of data from epidemiological, toxicological and controlled human exposure studies.
- **Susceptible groups.** Previous studies have only considered acute exposure effects in mild asthmatics. With regard to the studies on biological mechanisms, susceptible subgroups need to be identified, to be able to protect the most vulnerable part of the general population (Question C2).

2. Exposure assessment and monitoring

- **Improved assessments of exposure to outdoor versus indoor NO₂.** Determining separately the effects of indoor and outdoor exposure to NO₂ is a major issue. Co-pollutants that accompany NO₂ indoors and outdoors are likely to be different because the sources of NO₂ are different. There has always been a suspicion that co-pollutants formed alongside NO₂ in indoor air may be influential to health, and hence separate evidence from experimental and epidemiological studies of outdoor NO₂

exposures is required explicitly on the health effects, especially respiratory effects (Question C10).

3. Epidemiological studies

- **Direct effects of NO₂.** It was noted in Question C2 that there is a need to better understand whether NO₂ per se has direct effects on severe and hyperreactive asthmatics. More studies are therefore needed to verify whether NO₂ exerts a direct effect on human health at current ambient levels, acts as an indicator of other harmful components of the pollutant mix, and/or is a combination of these effects (Questions C2 and C8). This should be done by taking into consideration the variability of the mechanisms between population groups – for example, susceptible individuals as opposed to healthy volunteers.
- **Novel approaches.** New studies could, for example, take advantage of any changes in the ratio of NO₂ to primary PM metrics over time. Evaluation of recent data from epidemiological studies that use such novel approaches could allow the assessment of the relative importance of the adverse effects on health of NO₂ and other constituents of the traffic-dominated mix of ambient air pollutants (Questions C1 and C4), as well as the effect of the changing air pollution mix on the risk estimates for NO₂ of mortality (Question C4).

A workshop that focused specifically on research needs that relate to NO₂ and its effects on health was held in London, United Kingdom, in 2011. The report of the workshop also included a number of recommendations for future research (HPA, 2011).

Metals

The following gaps have been identified for the metals included in Question C5 (arsenic, cadmium, lead and nickel).

- **Arsenic.** The estimated cancer risk of inhalation of low levels of arsenic in ambient air is based on extrapolation from high-level exposure in a few occupational cohorts. While this is the standard technique, there is a need for further epidemiological evidence from cohorts at lower exposures, to assess the risk of low levels of arsenic in air.
- **Cadmium.** Several studies in the last couple of years have indicated the risk to the general population of atherosclerosis and cardiovascular disease from low levels of exposure to cadmium. If these reports mirror true causal associations, such effects may be as important for public health as effects on kidney and bone, so further epidemiological and experimental studies are needed. The rationale for limiting cadmium levels in air in the air quality guidelines is to decrease deposition of cadmium on soil, to avoid oral exposure, which is predominant. The quantitative association between cadmium in air and human dietary exposure needs to be elaborated.

- **Lead.** The causal chain between lead in air and adverse effects on children's cognition and behaviour needs better data on the estimated increase of lead in blood per unit increase of lead in air at current low levels of lead in air in Europe.
- **Nickel.** More epidemiological and experimental studies are needed on the possible association between nickel in ambient air and cardiovascular disease.

Of the metals not included in Question C5, the following may be important in terms of human exposure via ambient air.

- **Hexavalent chromium.** Its compounds are carcinogenic. Some studies have suggested that hexavalent chromium in ambient air could contribute substantially to the risk of lung cancer in the general population. The current WHO air quality guideline value was extrapolated from occupational exposure. Further studies are needed to establish whether hexavalent chromium at ambient levels in Europe poses a cancer risk.
- **Cobalt, iron, zinc, and possibly manganese.** These have the ability to form reactive oxygen species. The concentration of these elements in ambient air may contribute to PM toxicity. There is a need for more information and evaluation of this issue.
- **Manganese.** Exposure to manganese via inhalation is neurotoxic. The present WHO guideline value for ambient air is derived from occupational exposure data and uncertainty factors. Additional studies have emerged in the 2000s on occupational exposure, and there is a need for an evaluation of whether these studies should affect present risk assessment and guidelines.
- **Platinum.** For this, no specific guideline value was recommended by WHO in the past. Further studies were recommended, and this is still warranted.
- **Vanadium.** The guideline value was based on respiratory symptoms in occupationally exposed workers, after applying an uncertainty factor. An evaluation based on more recent data about effects in the general population would be appropriate.
- Considering the effects of metals (copper, zinc, iron and manganese) related to oxidative stress, relative to the biological potential of metals in different forms and/or states (such as platinum in catalysts and/or fuel additives; iron and antimony in brake pads), most of the evidence for toxicity related to environmental concentrations is indirect. There is a need to describe the health outcomes related to measurements of oxidative stress.
- Atmospheric speciation studies of metals, such as hexavalent chromium (chromium (VI)) versus chromium (III), should be carried out to evaluate (more specifically) the health outcomes.

PAHs

The following data gaps have been identified for PAHs.

- **Exposure–response functions.** Further research is needed to develop exposure–response functions that can be used to recommend exposure guidelines (Question C6).
- **Relative toxicities.** Relative toxicities of different compounds and mixtures (such as those derived from combustion of fossil fuel and biomass) need to be assessed (Question C6).
- **Suitability of benzo[*a*]pyrene as a marker.** Further studies to confirm the suitability of benzo[*a*]pyrene as a marker of the PAH mixture should be carried out. Occupational studies that are the basis of estimation of health risks do not provide this information.
- **Noncancer outcomes.** Noncancer outcomes need to be assessed further, based on existing studies that indicate that a number of noncancer health outcomes (reproductive, cognitive and respiratory) might be the consequence of airborne PAH exposure (Question C6). The effect of exposure to PAHs on gene expression and methylation needs further study.

SO₂

Specifically for SO₂, the following issues have been raised.

- Recent reanalysis of chamber study evidence suggests a non-significant difference between responders and non-responders at lower concentrations of SO₂ as part of a trend, with more significant differences occurring at higher concentrations. The answer to Question C7 suggests that further research to confirm whether or not this difference applies at lower concentrations would have implications for the 10-minute guideline.
- Further work is needed to identify the role of SO₂ per se at current ambient concentrations in Europe in triggering acute effects on mortality and morbidity
- Further chamber studies are needed to establish the appropriateness of the current 10-minute air quality guideline of 500 µg/m³ in protecting subjects with severe asthma.

Question C10

What is the contribution of exposure to ambient air pollution to the total exposure of air pollutants covered by the regulations, considering exposures from indoor environments, commuting and workplaces?

Answer

Tobacco smoke, where permitted indoors, dominates the exposure of the individuals to at least PM_{2.5} (and particle metrics black carbon and ultrafine particles), carbon monoxide, benzene, benzo[*a*]pyrene and naphthalene, and contributes also to exposure to NO₂. Tobacco smoke exposures and risks, however, are targeted in specific policies and not in ambient air policies, and therefore the other answers below refer to conditions free of tobacco smoke.

- In general, all exposures to air pollution of indoor and occupational origin, as well as exposure from commuting, vary between individuals much more than exposure to air pollution of ambient origin and depend strongly on the microenvironments and behaviour of the individual.
- Specifically, commuting can increase exposure to PM, NO₂, carbon monoxide and benzene, and it is a major contributor to exposure to ultrafine particles, black carbon and some metals – most importantly, iron, nickel and copper in underground rail transport systems.
- Individual industrial workday exposure levels may be orders of magnitude higher than the average population exposure levels, but as they affect only quite specific and controlled population subgroups and are controlled by occupational (and not ambient air pollution) policies, they are not covered in this chapter.
- Population exposure to NO₂ (where gas appliances are infrequent), PM_{2.5}, black carbon, ozone, carbon monoxide and SO₂ (with more limited evidence also concerning inhaled exposures to benzo[*a*]pyrene, arsenic, cadmium, nickel and lead) comes dominantly from ambient air and outdoor sources.
- Ambient air, indoor sources and commuting are all important for population exposure to NO₂, and (where gas appliances are frequent) benzene and naphthalene are also important.
- The high end of the individual exposures to PM_{10-2.5} and naphthalene come from indoor sources and commuting.
- Solid-fuel-fired indoor fireplaces and stoves, where used under suboptimal conditions, dominate the high end of exposures to PM_{2.5}, black carbon, ultrafine particles, carbon monoxide, benzene and benzo[*a*]pyrene of the individuals affected.

Rationale

General

On average, active adult urban populations in Europe spend an average 85–90% of their time indoors, 7–9% in traffic and only 2–5% outdoors (Hänninen et al., 2005; Schweizer et al., 2007). The most vulnerable groups, such as infants, toddlers, the elderly and the chronically ill, spend nearly 100% of their time indoors. By sheer time allocation, therefore, exposures indoors dominate total air pollution exposures. In the absence of indoor smoking and the burning of solid fuel, however, indoor exposures to most of the EU-regulated air pollutants are primarily due to outdoor sources from which the pollutants disperse via ambient air and penetrate into indoor spaces by air exchange, or are carried indoors as dust on shoes and clothes. For some pollutants, indoor and outdoor sources are of similar importance, and for yet others, the highest exposures and health risks arise from indoor sources, even though population average exposures arise mainly from ambient air.

The assessments in the current chapter refer to total exposure via inhalation to each of the contaminants through a population's daily activities and microenvironments, regardless of the source for (or location of) the exposure. For two reasons, the so-defined total exposure may not always be the most relevant metric for risk assessment or control: (a) although PM epidemiology demonstrates remarkable consistency for very different PM source mixtures and compositions, the same PM_{2.5} mass originating from different sources and of different composition is hardly identical in toxicity; and (b) the role of a pollutant as an indicator of a complex mixture is likely to be different when it originates from different sources, such as NO₂, indicating outdoor traffic exhaust rather than indoor gas appliances.

Tobacco smoke

Where smoking tobacco occurs indoors, it alone dominates the exposure of non-smoking individuals to PM_{2.5}, carbon monoxide, benzene, naphthalene and benzo[*a*]pyrene, and contributes also to their exposure to NO₂. Keeping this in mind, all of the following pollutant-by-pollutant assessments apply only to tobacco-smoke-free indoor environments.

Summary table

For each of EU-regulated air pollutant, Table 12 summarizes: (a) the most important and common non-ambient sources; (b) their significance for high end individual exposure (and respective risks) and relative population-level contributions (of); (c) indoor and (non-industrial) occupational sources; (d) commuting exposure; (e) population exposure to ambient air; (f) the proportion of population exposure influenced by ambient air regulation; and (g) the reduction in population exposure due to a given reduction in the amount of ambient air pollution.

For ozone, for example, Table 12 shows that its indoor sources are rare (such as ozonators) or weak (laser printers), and ambient air dominates the population exposure, of which almost all is, therefore, influenced by ambient air policies. However, because ozone infiltration from ambient to indoor air is generally low, a $10 \mu\text{g}/\text{m}^3$ reduction in ambient air ozone concentration reduces the average population exposure concentration by less, $2\text{--}7 \mu\text{g}/\text{m}^3$.

The table generalizes large quantities of often inconsistent data compiled from all of the articles cited. It does not necessarily apply to all individual conditions and should, consequently, be interpreted with caution.

Table 12. Most important and common non-ambient sources of air pollutants

Data quality range for pollutant: Good *** Average ** Poor * Nil ^o	Indoor and common occupational sources for personal air pollution exposure (in addition to tobacco)	Significance of the highest individual exposure	Contribution to population air pollution exposure (%)			Proportion of population exposure influenced by ambient policy (%)	Population exposure reduction due to 10 µg/m ³ ambient reduction
			Indoor and occupational origin	Commuting exposures	Ambient air origin		
PM _{2.5} ***	Solid fuel combustion, candles	Dominant	20-50	35	40-70	50-80	6-8 µg/m ³
PM _{10-2.5} ^o			Up to 80	Up to 50	Up to 25	Up to 40	2-3 µg/m ³
Ozone **	Ozonators, electrostatic air cleaners, laser printers	Rare or weak	Nil	Nil	Ca. 100	100	3-6 µg/m ³
NO ₂ **	Unvented gas appliances	Significant	Up to 50	Up to 20	40-90	50-100	7-9 µg/m ³
Carbon monoxide**	Unvented, faulty and/or improperly operated combustion equipment	Dominant	Some	Some	Up to 90	Up to 90	10 µg/m ³
SO ₂ ^o	Residential coal burning, paraffin heaters and lamps	Rare, but dominant	Nil	Nil	Up to 100	Up to 100	4-7 µg/m ³
Benzene***	Attached garages and solvents in some domestic chemicals	Dominant	Up to 50	Up to 25	Up to 80	50-90	Up to 10 µg/m ³
Benzo[a]pyrene*	Solid fuel combustion - naphthalene also in mothballs and coal-tar-based waterproofing	Dominant	Small	Small	Up to 100	Up to 100	6-8 µg/m ³
Naphthalene**		Rare, but dominant	40-70	Small	30-60	30-60	< 10 µg/m ³
Arsenic ^o Cadmium ^o Nickel ^o Lead*	Some old paints and accumulated dust	Some	Up to 40	Nil	Up to 90	60-90	See PM _{2.5}
Mercury ^o	Broken thermometers and fluorescent tubes, amalgam fillings	High	Up to 65	Nil	< 100	< 100	< 10 µg/m ³

PM_{2.5} and PM_{10-2.5}

Indoor exposure to PM of ambient origin and commuting exposure (excess exposure relative to outdoor air while in transit) dominate the population exposure to PM_{2.5}. On average, outdoor air PM_{2.5} is responsible for 40–70% of the total population exposure to PM_{2.5}. Ambient air PM_{2.5} policies affect 60–80% of the urban population exposure, which consists of exposure to PM_{2.5} of ambient origin that penetrates indoors, the part of commuting exposure influenced by ambient air policies, plus exposure during the time spent in outdoor environments. An ambient air PM_{2.5} reduction of 10 µg/m³ reduces the average population exposure concentration by 5–8 µg/m³ – less than the 10 µg/m³ ambient reduction because, on average, only 40–70% of ambient air PM_{2.5} penetrates into indoor spaces where people spend an overwhelming proportion of their time. The average PM_{2.5} infiltration into buildings decreases steadily as new, sealed and air-conditioned buildings replace the older building stock (Chen & Zhao 2011; Hänninen et al., 2004a,b; Koistinen et al., 2004; Lai et al., 2004; Lanki et al., 2007; Johannesson et al., 2007; Fromme et al., 2008; Wichmann et al., 2010; Hänninen et al., 2011; Gariazzo et al., 2011; Oeder et al., 2012).

The mean excess PM_{2.5} exposure levels, while commuting, range from negligible in modern cars, buses and trams with intake air filtration, up to 20–30 µg/m³ when exposed directly to busy street air in vehicles with open windows, at bus stops, in metro stations and tunnels, or when walking or biking. The contribution of commuting to the total daily exposure therefore depends on the means, time and route. No studies representative of the population were found that would report commuting exposures in the context of total exposure and ambient air concentrations (Adams et al., 2001; Riediker et al., 2003; Seaton et al., 2005; Aarnio et al., 2005; Fondelli et al., 2008; Asmi et al., 2009; Grass et al., 2009).

On average, about half of ambient air PM₁₀ is PM_{2.5}. Ambient PM₁₀ policies reduce population exposures mainly via their impacts on the fine PM fraction, but have a smaller impact on the exposure to the coarse PM fraction, of which a large proportion originates from indoor sources (Chen & Zhao, 2011; Hänninen et al., 2011; Gariazzo et al., 2011).

Ozone

Indoor ozone sources are infrequent (ozonators, old electrostatic air cleaners) or weak (laser printers). Indoors as well as outdoors, therefore, ozone of ambient origin is responsible for almost all of the population exposure, and ambient air ozone policies affect nearly all of the urban population exposures. Ozone is the most reactive of the EU-regulated air pollutants and, therefore, much of the ozone is lost in air exchange, in ventilation systems and in reactions with indoor surfaces and co-pollutants. Consequently, the average indoor air ozone levels are only 20–50% of the ambient air levels, and a given ambient air ozone reduction (µg/m³) results in a much smaller population exposure reduction.

The broader air pollution exposure impact of ozone policies may be more significant for reducing some irritating and toxic products of atmospheric ozone chemistry, as well as

reactions with indoor air co-pollutants and dust on air filters in ventilation systems (Blondeau et al., 2005; Weschler, 2006; Bekö et al., 2006; Baxter et al., 2007).

NO₂

Where present, indoor sources of NO₂, most importantly unvented gas appliances, may significantly increase individual exposures. Indoors, NO₂ is a moderately reactive gas and, consequently, the indoor concentration stays substantially below the ambient air concentration, except when emissions from gas appliances increase them to (and even above) the ambient air concentration level. Without indoor sources, the population exposure to NO₂ is dominated primarily by NO₂ of ambient origin and secondarily by commuting exposure. Ambient NO₂ policies affect from 50% (with gas appliances) to 100% (no gas appliances) of the NO₂ exposures and reduce the exposure by 50–80% (depending on region and season) of the reduction in the ambient concentration (Monn, 2001; Kousa et al., 2001; Lee et al., 2002; Lai et al., 2004; Baxter et al., 2007; Kornartit et al., 2010).

Carbon monoxide

Indoor sources and unvented, faulty and/or incorrectly operated combustion equipment are responsible for (almost) all high level exposures to carbon monoxide. Otherwise, almost all of the population exposure to carbon monoxide originates from commuting – which was much more significant in the past – and from ambient air. In Milan, Italy, in 1996–1997, the average exposure concentration of 2.1 mg/m³ was attributed to ambient air (84%), residential indoor sources (4%), occupational indoor sources (3%), excess concentrations during transport (8%), and other sources (1%) (Bruinen de Bruin et al., 2004). Current ambient air carbon monoxide policies affect almost all of the total urban population exposure and reduce the exposure by 100% of the ambient air concentration reduction.

Current urban ambient air carbon monoxide levels are an order of magnitude below the EU air quality standards. The still frequent and often lethal carbon monoxide intoxications and the indoor sources and levels of carbon monoxide that cause them, however, are not related to ambient air carbon monoxide concentrations or affected by policies. (Alm et al., 2001; Braubach et al., 2013)

SO₂

Indoor sources, residential coal burning, unvented paraffin lamps and heaters still dominate some exposures of some individuals to SO₂. In current European urban environments, however, indoor sources that would significantly influence the population exposure to SO₂ are rare. Consequently, ambient air SO₂ policies are effective in reducing the indoor air concentrations and exposures.

Benzene

Benzene-containing organic solvents, in interior materials and household chemicals, are being increasingly restricted by regulations, but still remain significant for exposures in

some European regions. Airborne benzene of indoor – most importantly from attached garages – and outdoor-origin and commuting exposures are all relevant for population exposures. Ambient air benzene policies affect from 50% (with indoor sources) to 90% (no known indoor sources) of the average urban population exposure and reduce the exposure by almost all of the ambient air concentration reduction (Cocheo et al., 2000; Edwards & Jantunen; 2001; Ilacqua & Jantunen, 2003; Lai et al., 2004; Pérez-Ballesta et al., 2006; Kotzias et al., 2009; Delgado-Saborit et al., 2009; Sarigiannis et al., 2011).

PAHs: naphthalene and benzo[*a*]pyrene

Most of the naphthalene in air is in the vapour phase, and all benzo[*a*]pyrene, instead, is in the particle phase. Solid fuel combustion remains a significant indoor source of both benzo[*a*]pyrene and naphthalene. Naphthalene has also other indoor sources, such as naphthalene mothballs and coal tar based waterproofing. All high-end exposures are caused by indoor sources.

In the absence of indoor solid fuel combustion, all exposure to benzo[*a*]pyrene is of ambient origin. The contribution of ambient air to the exposure of the population to naphthalene is 30-60%. Benzo[*a*]pyrene infiltration follows the infiltration of PM_{2.5}. Policy impacts should, therefore, also be similar in terms of the reduction of exposure due to the reduction of ambient air concentration. Naphthalene infiltration is similar to the infiltration of benzene, and the impact of policies should also be similar (Jantunen et al., 1999; Gustafson, Ostman & Sällsten, 2008; Ravindra, Sokhi & Van Grieken, 2008; Delgado-Saborit, 2009; Jia & Batterman, 2010; Sarigiannis et al., 2011; Yazar, Bellander & Merritt, 2011).

Arsenic, cadmium and lead

In relation to ambient air, there appear to be significant indoor sources of arsenic, cadmium and lead that contribute to indoor air, because their indoor levels often exceed the ambient air concentrations. Infiltration of these elements from ambient to indoor air is likely to follow closely the infiltration of PM_{2.5}. Policy impacts should, therefore, also be similar in terms of the reduction of exposure and the reduction of ambient air concentration (Hänninen et al., 2004a; Lai et al., 2004; Komarnicki, 2005).

These elements enter from the outdoor to the indoor environment not only in airborne particles, but also with dust, which may be a more significant exposure pathway – for toddlers, in particular – and it warrants a different regulatory approach.

Mercury

Mercury in indoor air is mainly in the vapour phase. The greatest sources of mercury in indoor air are broken mercury-filled thermometers or barometers. The common indoor sources are broken fluorescent tubes (short peak exposures) and amalgam fillings (long-term low-level exposures). The exposure contribution of these common indoor sources to long-term exposure may be of the same order as the contribution from ambient air.

D. General questions

Question D1

What new information from epidemiological, toxicological and other relevant research on health impacts of air pollution has become available that may require a revision of the EU air quality policy and/or WHO air quality guidelines notably for PM, ozone, NO₂ and SO₂?

Answer

Introduction

Since the publication of the 2005 global update of the WHO air quality guidelines, a considerable amount of new scientific information has appeared on all four pollutants – PM, ozone, NO₂ and SO₂ – discussed in this part of the report. In many cases, these have shown associations with adverse health outcomes at pollutant levels lower than those in the studies on which the 2005 global update of the WHO air quality guidelines were based. This is particularly true for PM, ozone and NO₂. In light of this, we would recommend that WHO begins the process of developing revisions to the earlier guidelines, with a view to completing the review by 2015. We would further recommend that the EC ensures that the evidence on the health effects of air pollutants and the implications for air quality policy are reviewed regularly.

The following is a short summary of thoughts about and the needs and recommendations for the four pollutants.

1. PM

- There is a need to revise the current WHO air quality guidelines for PM₁₀ (20 µg/m³, annual average; and 50 µg/m³, 24-hour average, 99th percentile) and PM_{2.5} (10 µg/m³, annual average; and 25 µg/m³, 24-hour average, 99th percentile).

The current state of scientific knowledge, supported by a large body of new studies, shows a wide range of adverse effects on health associated with exposure to PM_{2.5} (see answers to Question A1) and PM₁₀ (see answers to Question A4). The data strongly suggest that these effects: have no threshold within the ambient range studied; follow a mostly linear concentration–response function; and are likely to occur at fairly low levels, close to PM_{2.5} background concentrations. The scientific basis for the WHO air quality guidelines for PM_{2.5} and PM₁₀ and the corresponding interim targets (all set in the 2005 global update of the WHO air quality guidelines) are therefore now even stronger than 7 years ago. The WHO air quality guideline values set in 2005 include no margin of safety. In 2005 the WHO air quality guideline values were set to reflect levels close to the lower end of the available concentration–response functions at that time; there now exists more recent information at lower PM

levels than existed previously.

- In the same perspective, there is a strong need to re-evaluate and lower at least the limit value of the second stage for PM_{2.5} of 20 µg/m³ (annual average, to be met by 2020) set in Section D, Annex XIV of Ambient Air Quality Directive 2008/50/EC.

At the moment, there is a considerable gap between the WHO air quality guidelines for PM_{2.5} (10 µg/m³, annual average), the PM_{2.5} United States standard set in 2012 (12 µg/m³, annual average), the EU limit value to be met in 2015 (25 µg/m³, annual average) and the EU Stage 2 indicative limit value (20 µg/m³). There is a need for an additional PM_{2.5} short-term (24-hour) limit value (as suggested in the Answer to Question A3) and a re-evaluation of the PM₁₀ limit values.

The scientific support for the exposure-reduction approach to managing PM air quality incorporated in Directive 2008/50/EC (EU, 2008) has been strengthened, and this approach provides, in principle, a preferable way to reduce the health impacts of PM_{2.5}. Irrespective of the actual concentration or a specific limit or target value, enforcing national exposure reduction targets, such as the one found in Section B, Annex XIV of the Directive, will lead to health benefits at the population level.

- It would be advantageous to develop an additional air quality guideline to capture the effects of road vehicle PM emissions not well captured by PM_{2.5}, building on the work on black carbon and/or elemental carbon (*Health effects of black carbon*; Janssen et al., 2012) and evidence on other pollutants in vehicle emissions.
- Besides the public health and/or air quality concerns, black carbon is also an important short-lived climate forcer, which contributes to the warming of the Earth's atmosphere. Reducing black carbon emissions and concentrations is beneficial for population health and, for sources with high black carbon/organic carbon ratios, helps to mitigate short-term climate change.
- Although there is considerable evidence that ultrafine particles can contribute to the health effects of PM, for ultrafine particles (measured by the number of particles) the data on concentration–effect functions are too scarce to evaluate and recommend an air quality guideline. The same evaluation applies for organic carbon. Current efforts to reduce the numbers of ultrafine particles in engine emissions should continue, and their effectiveness assessed, given the potential health effects.
- Given the significant short- and long-term adverse effects on health identified as being caused by exposure to PM_{2.5}, the National Emissions Ceiling Directive should be revised to include a ceiling for PM_{2.5}. It is of the utmost importance to reduce emissions from vehicles and from combustion of liquid and solid fuels, including non-road mobile machinery and biomass burning, in achieving the ceiling in a revised National Emissions Ceiling Directive and also in achieving limits for PM in the Ambient Air Quality Directive.

- Another appropriate goal is to reduce non-tailpipe emissions from road traffic, given the increasing relative contribution of non-tailpipe emissions when vehicle exhaust emissions are reduced.

2. Ozone

- With regard to ozone, the most important policy-related issues are the recent emergence of evidence for effects of long-term (months to years) exposures and the existence (or otherwise) and concentration level of a threshold below which effects are unlikely in the general population. Long-term ozone concentrations are determined by hemispheric or global emissions of precursor pollutants. If a no-effect threshold concentration does not exist, or is very low, and hypothetically assuming a linear dose–response function through the origin, total annual health impacts will be proportional to annual mean ozone concentrations and will be much larger than otherwise, with similar policy implications for regional versus global hemispheric controls.
- In light of the answers to Questions B1–B4, guidelines for long-term average ozone concentrations should be considered.
- Analysis of the extent to which current or foreseen policies within the EU or the CLRTAP Gothenburg Protocol (which covers a wider geographical area) are sufficient to reduce long-term average ozone concentrations may help dictate the appropriate course of action for engaging with other major emitters in the northern hemisphere. This is needed to consider possible actions to reduce these longer-term ozone concentrations, possibly using the CLRTAP Task Force on Hemispheric Transport of Air Pollution (co-chaired by the EU and the United States) to guide the discussions. Reductions of methane within and outside the EU would be beneficial in reducing long-term average ozone concentrations.
- The Answer to Question B2 concluded that evidence for a short-term threshold is not consistent but, where a threshold is observed, it is likely to lie below $90 \mu\text{g}/\text{m}^3$ (maximum 1-hour mean). In performing health impact assessments the use of SOMO35 and SOMO10 has been recommended for short-term effects. For long-term effects, the Answer to Question B2 recommended a health impact assessment as a sensitivity scenario.
- Given the emerging evidence discussed in the answers to questions B, and pending the outcome of the health impact assessment, a long-term target value, possibly as a summer (April to September inclusive) mean for which evidence is stronger than for an annual mean, could be considered in the future by the EC.

3. NO₂

- Since the release of the 2005 global update of the WHO air quality guidelines, new epidemiological studies have emerged, reporting associations with both short-term and long-term exposures to NO₂. Some of these, notably the short-term studies, report associations that are robust to inclusion of other pollutants.
- Many of these studies were in areas where concentrations were at or below the current EU limit values.
- The results of these new studies provide support for updating the current WHO air quality guidelines for NO₂, to give: (a) an epidemiologically based short-term guideline; and (b) an annual average guideline based on the newly accumulated evidence from outdoor studies. In both instances, this could result in lower guideline values.
- There is consistent short-term epidemiological evidence and some mechanistic support for causality, so that it is reasonable to infer that NO₂ has some direct effects. However, as with the short-term effects, NO₂ in the long-term epidemiological studies may represent other constituents. Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations is suggestive of a causal relationship.
- There is no *health-based* case for either increasing or removing the NO₂ limit values in the EU Directive. Depending on the outcome of any revision of the WHO air quality guidelines for NO₂, there could then also be a case for the EU to consider revising the Directive limit values.
- There is no evidence to suggest changing the averaging time for the short-term EU limit value, which is currently 1 hour.

4. SO₂

- There is a need to revisit the evidence base for setting the WHO air quality guidelines for SO₂ (very short-term and short-term).
- Since the 2005 global update of the WHO air quality guidelines, some new studies on toxicological and health effects of SO₂ have been published. A reanalysis of the previous chamber study literature suggests a need to consider whether to increase the safety factor for the 10-minute guideline. For the 24-hour average guideline, the new studies give similar results to the previous studies. The new studies were conducted at a similar range of concentrations as the previous studies, so the 24-hour average guideline does not need to be changed if using the same method (using a concentration at the low end of the range of concentrations observed in the studies) to

set the guideline (Answer to Question C7). However, the evidence should be looked at again.

Rationale

1. PM

The evidence on airborne PM and public health is consistent in showing adverse effects on health at exposures experienced by urban populations in cities throughout the world, in both high-income and middle- and low-income countries. The range of effects is broad, affecting the respiratory and cardiovascular systems and extending to children and adults and to a number of large susceptible groups within the population, not to mention the newer evidence on intrauterine growth and neurocognitive effects. Overall, the evidence for adverse effects on health from PM has strengthened since the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006). The risk for various outcomes has been shown to increase with exposure, and the available evidence does not suggest a threshold below which no adverse effects would be anticipated – and there is little possibility of there ever being such evidence. Indeed, the lower range of concentrations at which adverse effects have been demonstrated is not greatly above rural background concentrations, which was estimated at 3–5 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ in western Europe and the United States. The epidemiological evidence shows adverse effects of particles after both short-term and long-term exposures. Given these findings, not only may the WHO guidelines for PM need to be revised, but the Stage 2 indicative limit value in EU Directive 2008/50/EC (currently 20 $\mu\text{g}/\text{m}^3$) may need to be re-evaluated and lowered.

Since the 2005 global update of the WHO air quality guidelines, many new studies from around the world have been performed and published. These studies strengthen the evidence of a linear concentration– (exposure–)effect relationship without a threshold for various health outcomes associated with exposure to $\text{PM}_{2.5}$ and PM_{10} (see answers to Questions A1, A4, and A5). The scientific literature shows also that PM_{10} is not just a proxy measurement for $\text{PM}_{2.5}$. Coarse and fine particles deposit mostly at different locations in the respiratory tract. The finer the particles are the deeper they can penetrate into the lungs. Independent effects of the coarse fraction are seen in epidemiological studies. The effects of $\text{PM}_{\text{coarse}}$ (10–2.5 μm) and PM_{fine} (2.5 μm) may be related to different mechanisms (see Answer to Question A4). $\text{PM}_{\text{coarse}}$ and PM_{fine} have different sources too, and the dispersion gradient near the source is different.

In light of this strengthening of evidence, there are therefore good grounds to revise the current WHO air quality guidelines for PM_{10} and $\text{PM}_{2.5}$. There is also a need to re-evaluate and lower the indicative Stage 2 limit value for $\text{PM}_{2.5}$ of 20 $\mu\text{g}/\text{m}^3$ annual average in the EU Directive due to be met in 2020. There is a considerable gap between this number and the WHO annual average guideline of 10 $\mu\text{g}/\text{m}^3$. There is also a gap between the EU limit value and the recently revised United States National Ambient Air Quality Standards value of 12 $\mu\text{g}/\text{m}^3$ annual average, to be attained by 2020 with a possible extension to 2025 in certain circumstances. There have been differences in

stringency between the implementation of the United States and EU so-called headline figures in the past, which make a direct comparison more challenging. However, some factors that lead to difference between EU and United States legislation have been removed by the requirement in the United States that the revised PM_{2.5} standard (and the recently promulgated hourly NO₂ standard) should be assessed near busy roads. One particular difference remains: the United States annual and daily standards are averages over 3 years, whereas the EU limit value for PM_{2.5} applies to a single year. This is not likely, however, to substantially change the actual application of the limit values, leaving the significant gap between the EU limit value and that of the United States National Ambient Air Quality Standards noted above.

The Ambient Air Quality Directive (2008/50/EC), besides setting PM_{2.5} target and limit values, requires Member States to reduce the PM_{2.5} population exposure by means of non-mandatory national exposure reduction targets and a mandatory exposure concentration obligation. The rationale for this was based on the conclusion that any threshold for adverse effects of PM_{2.5} was likely to be very low or even zero. The evidence for the adverse effects of PM and the concept of a very low threshold have strengthened since the Directive was agreed upon, and so there is even more scientific support for the exposure-reduction approach to managing PM air quality. The magnitude of the required reduction depends on the value of the calculated average exposure indicator, expressed in µg/m³. The indicator is based on PM_{2.5} measurements in urban background locations and is assessed as a three-calendar year running annual mean averaged over all stations. The national PM_{2.5} exposure reduction target for the protection of human health (Annex XIV, Section B of Directive 2008/50/EC) relative to the average exposure indicator in 2010 depends on the initially calculated concentration – for example, if the concentration calculated for 2009, 2010 and 2011 is in between 13 µg/m³ and 18 µg/m³, the reduction target is 15%. If the initial value is higher, the required percentage reduction is higher and vice versa. The national exposure reduction target provides, in principle, a more powerful approach to the improvement of air pollution-related effects on health and, hence, the authors recommend that the national exposure reduction strategy be set as mandatory legislation by 2020. Irrespective of the actual concentration or a specific limit or target value, population health benefits from lower PM average exposure.

It is evident that not all components of the PM mixture are equally toxic (see Answer to Question A2 as a starting point). It is relatively straightforward to show differences in toxicity in experimental chamber studies with individual components of the mixture in isolation. But in a real everyday situation, the population is exposed to a complex mixture of hundreds of particle-bound and gaseous components. These components interact, and additional or synergistic effects of exposure are possible. By means of epidemiological studies, it is difficult to allocate an observed effect to a single component of the PM-gas mixture. Many studies, however, show that living near traffic represents an increased health risk. The health effects observed were consistent after adjusting for socioeconomic status and for noise (see Answer to Question C1). These risks are unlikely to be explained by PM_{2.5} mass alone, since PM_{2.5} mass is only slightly elevated close to roads with a heavy traffic load. In contrast, levels of pollutants – such as ultrafine particles, elemental carbon and/or black carbon, PAHs, some metals, carbon monoxide, nitric oxide and NO₂

and, to some extent, PM₁₀ and organic carbon – are more elevated near roads. Carbon monoxide, NO₂ and PM₁₀ are already regulated by ambient air quality limit values, but for fine traffic exhaust PM, or other primary combustion PM, there is no legally binding ambient air quality regulation. Hence, there is a strong case for regulating primary PM emissions from combustion sources (particularly traffic) in the ambient atmosphere.

Many studies have suggested that elemental carbon mass (unit: µg/m³) and black carbon (measured by absorption, and elemental carbon scaled by local random sampling) may be useful in representing traffic PM exhaust. In 2011, the Joint WHO/CLRTAP Task Force on Health Aspects of Air Pollution made a systematic review of the evidence of the health effects of black carbon and published, in 2012, the report *Health effects of black carbon* (Janssen et al., 2012). The report concluded:

That short-term epidemiological studies provide sufficient evidence of an association of daily variations in BC [black carbon] concentrations with short-term changes in health (all-cause and cardiovascular mortality, and cardiopulmonary hospital admissions). Cohort studies provide sufficient evidence of associations of all-cause and cardiopulmonary mortality with long-term average BC exposure. Studies of short-term health effects suggest that BC is a better indicator of harmful particulate substances from combustion sources (especially traffic) than undifferentiated PM mass.

The evidence for the relative strength of associations from long-term studies is inconclusive. The Joint WHO/CLRTAP Task Force on Health Aspects of Air Pollution review of the results of all available toxicological studies suggested that: “BC [black carbon] may not be a major directly toxic component of fine PM, but it may operate as a universal carrier of a wide variety of chemicals of varying toxicity to the lungs, the body’s major defence cells and possibly the systemic blood circulation”.

Health effects associated with exposure to PM_{2.5} and PM₁₀ are usually also associated with black carbon particles (and vice versa) in studies where all three metrics were evaluated. Effect estimates (from both short- and long-term studies) are much higher for black carbon than for PM₁₀ and PM_{2.5} when the measurements are expressed per unit of mass concentration (µg/m³); they are, however, generally similar per interquartile range in pollutant levels. In multipollutant models used in these studies, the black carbon effect estimates are robust to adjustment for PM mass, whereas PM mass effect estimates decreased considerably after adjustment for black carbon. The evidence from long-term studies is inconclusive: in one of the two available cohort studies, using multipollutant models in the analysis, the effect estimates for black carbon are stronger than those for sulfates, but the opposite (in the strength of the relationship) is suggested in the other study. There are not enough clinical or toxicological studies to allow for: an evaluation of the qualitative differences between the health effects of exposure to black carbon and PM mass; a quantitative comparison of the strength of the associations; or identification of any distinctive mechanism of black carbon effects.

The Task Force on Health agreed that a “reduction in exposure to PM_{2.5} containing BC [black carbon] and other combustion-related PM material for which BC is an indirect

indicator should lead to a reduction in the health effects associated with PM". The Task Force recommended that PM_{2.5} should continue to be used as the primary metric in quantifying human exposure to PM and the health effects of such exposure, and for predicting the benefits of exposure reduction measures. The use of black carbon may be very useful in evaluating local action aimed at reducing the population exposure to combustion PM – for example, from motorized traffic. There is currently no regulatory pressure relating to primary PM exhaust emissions in the Ambient Air Quality Directive (2008/50/EC). As it is too early to suggest a target, indicative or (even) limit value for black carbon in the EU Ambient Air Quality Directive, the previous work by the Joint WHO/CLRTAP Task Force on Health Aspects of Air Pollution is a good basis for WHO to consider developing a guideline for black carbon, or for another component of primary vehicle emissions. The EU Ambient Air Quality Directive already requires monitoring elemental carbon and organic carbon at rural background sites. This could be extended to include urban areas.

In addition to PM₁₀, PM_{2.5} and black carbon, the effects related to the number of ultrafine particles have also attracted significant scientific and medical attention. There is a considerable body of scientific literature that addresses the health effects related to the number of particles. In short-term studies, some effects on different health outcomes have been seen, but studies on long-term effects are virtually absent. The scientific base is too small to work on a guideline for the number of ultrafine particles and to propose a guideline value. The measurement techniques for the number of ultrafine particles are not as advanced and harmonized as those for PM₁₀, PM_{2.5} or black carbon, and the quality of the existing data may be variable and not comparable directly.

Nevertheless, it could be useful in the future to have some data for particle numbers, to look for variations in time and space (which can be very large), and so have information on possible trends, and to compare the number of ultrafine particles with the number of black carbon particles – to check if black carbon is also a good marker for the number of ultrafine particles. In contrast to ambient air quality monitoring, harmonized methods are available to check for the number of particles directly in diesel or gasoline exhaust. In the Euro 5 (diesel passenger cars) and Euro 6 (heavy duty vehicles) regulations, a particle number norm has been set to complement the existing mass (PM) standard. Particle number standards allow the efficiency of different particle filter systems to be checked, as the PM mass in the exhaust is already very low.

Many studies show that the organic carbon components of the PM mixture (primary emitted organic carbon and secondary organic aerosols) may also have large health impacts. Many scientists consider that organic carbon or total carbon, as well as non-mineral carbon, may be a better air quality parameter than black carbon, especially for the near future. But techniques to measure primary organic carbon, secondary organic aerosols and total carbon are not advanced enough to be used in larger epidemiological studies. While it is possible to determine elemental carbon with adequate accuracy when using a strict temperature protocol, good discrimination between elemental carbon and organic carbon is more difficult and demanding. A more or less reproducible routine measurement for organic carbon is not available, and organic carbon population exposure

cannot be assessed satisfactorily. The published organic carbon epidemiology is more difficult to interpret than elemental carbon and/or black carbon epidemiology. Organic carbon dose– and/or concentration–effect functions are scarce. On the other hand, especially in summer in southern countries, organic carbon and secondary organic aerosol compounds arise not only anthropogenically, but also arise from natural biogenic sources, such as from pine trees (terpenes), and play an important role. Thus, at the moment, we do not have enough data on which to base a recommendation for an organic carbon guideline value. Organic carbon components can represent a significant part of PM_{2.5} mass, which is already regulated.

Besides black carbon (as a carrier of more toxic substances), evidence is also emerging for other components of the PM mixture being more toxic than others. At this stage, however, there is insufficient evidence to allow guidelines, target values or limit values to be set for other components. There are already suggestions from Member States that the number of limits and/or targets even for PM mass is too large and that they should be simplified. However, enough evidence is emerging to allow some policy advice to be given. This could be directed at the National Emissions Ceilings Directive (2001/81/EC) and also at the Ambient Air Quality Directive. The National Emissions Ceiling Directive could, in the future, incorporate a ceiling for primary emissions of PM_{2.5}, as has been done in the CLRTAP Gothenburg Protocol.

In achieving the ceilings for PM_{2.5}, reducing emissions from sources identified in the Answer to Question A2 – namely, from vehicles and the combustion of liquid and solid fuels, including biomass and their use non-road mobile machinery – is a priority. Moreover, emissions from tyre and brake wear are also emerging as being particularly toxic, and there is currently no policy addressing these. Member States could be required to monitor black carbon and/or elemental carbon and ultrafine particles (number of particles) at some urban sites (which is a chicken–egg problem for impact-related studies) and at traffic-exposed sites as a benchmark for abatement strategies. Similarly, in taking measures to achieve the obligations on PM mass (PM₁₀ and PM_{2.5}) in the Ambient Air Quality Directive, prioritizing the reduction of emissions from potentially more harmful sources can be fruitful.

Current scientific evidence implies that guidelines and standards cannot be proposed that will lead to complete protection against the adverse effects on health of PM, as thresholds have not been identified and the complete elimination of anthropogenic PM is not feasible. Rather, the standard setting process needs to achieve the lowest concentrations possible in the context of local constraints, abilities and public health priorities. The assessment of quantitative risk offers one approach to compare alternative scenarios of control and for estimating the residual risk with achieving any particular guideline value. Countries are encouraged to consider an increasingly stringent set of standards, which would include tracking progress through emission reductions and declining concentrations of PM. To the extent that the health effects associated with ambient PM have been reported at relatively low ambient concentrations, and since there is substantial interindividual variability in exposure and response in a given exposure, it is unlikely that any PM standard or guideline will provide universal protection for every individual

against all possible PM-related effects.

Black carbon and climate change

In 2011, the United Nations Environment Programme and the World Meteorological Association published the report *Integrated assessment of black carbon and tropospheric ozone: summary for decision makers* (UNEP & WMO, 2011). The main messages of the report are:

- Black carbon and ozone in the lower atmosphere are harmful air pollutants that have substantial regional and global climate impacts. They disturb tropical rainfall and regional circulation patterns, such as the Asian monsoon, affecting the livelihoods of millions of people.
- Black carbon, a component of PM, and ozone both lead to adverse impacts on human health, leading to premature deaths worldwide.
- Scientific evidence and new analyses demonstrate that control of black carbon particles and tropospheric ozone through rapid implementation of proven emission reduction measures would have immediate and multiple benefits for human well-being.

The measures identified in the report complement, but do not replace, anticipated carbon dioxide reduction measures. It is worth noting that black carbon is almost always emitted in conjunction with organic carbon. While black carbon is considered to have a warming effect in the atmosphere, organic carbon has the opposite effect (although even organic carbon can have a warming effect when deposited on snow and ice). Reductions in emissions from sources with relatively high black carbon/cooling aerosol ratios, as required by the CLRTAP Gothenburg Protocol, should therefore have beneficial effects on health and on the global climate. A recent paper (Bond et al., 2013) noted that reducing all emissions from the use of diesel and possibly residential biofuels would lead to a cooling effect.

2. Ozone

Averaging time of exposure

Ozone is a unique pollutant, in that concentrations over different averaging times are determined by different dominant mechanisms and sources, and hence with correspondingly different policy responses. High short-term peak hourly and 8-hourly concentrations in so-called smog episodes, lasting typically for a few days, are determined by regional precursor emissions and photochemical processes acting over typical scales of 100–1000 km. In the EU, this means policies to reduce precursor emissions need to be regional, in such instruments as the National Emissions Ceilings Directive and the CLRTAP Gothenburg Protocol. Peak hourly concentrations in smog episodes contribute relatively little to annual or 6-month averages, and these concentrations are determined in the EU largely by emissions over the northern

hemisphere or even the globe. Methane is the dominant agent in determining such longer-term concentrations.

Reducing peak hourly or 8-hourly smog episode concentrations, or reducing longer-term averages, therefore requires quite different policy responses.

Until now, evidence for the adverse effects of ozone has been for short-term exposures, either in chamber studies (typically up to 8 hours or so exposure times) or from time-series epidemiological studies that used various metrics relating to short-term ozone concentrations, and policy targets have been set accordingly. To protect human health, the EU Ambient Air Quality Directive has a target value for ozone expressed in terms of the maximum daily 8-hour mean ($120 \mu\text{g}/\text{m}^3$, not to be exceeded more than 25 times a year). The National Emissions Ceiling Directive and the Gothenburg Protocol have been successful in reducing peak ozone concentrations in Europe over the past two decades (Derwent et al., 2010).

Evidence for or against a threshold for short-term effects has been mixed and inconclusive, and various approaches have been taken in health impact assessments. Some have performed impact assessments with and without a threshold (DEFRA, 2007), while others have recommended using a cut-off. For example, a WHO-CLRTAP report recommended the use of SOMO35, on the basis that the relationships between ozone and adverse effects, and atmospheric models, were very uncertain below the $70 \mu\text{g}/\text{m}^3$ (35 ppb) hourly mean.

Evidence has now emerged, since the 2005 global update of the WHO air quality guidelines, for effects of ozone over longer periods of exposure, which has implications for policy, as described above. The study by Krewski et al. (2009), in a follow-up analysis of the American Cancer Society cohort, found the association between mortality and summer average ozone levels (calculated from concentrations measured from April to September 1980) was small, but significant, for deaths from all causes (HR: 1.02; 95% CI: 1.01–1.03) and from cardiopulmonary disease (HR: 1.03; 95% CI: 1.02–1.04). Using the annual average ozone concentration for 1980 resulted in non-significant associations with all-cause mortality and associations with cardiopulmonary mortality that were just significant (HR: 1.01; 95% CI: 1.00–1.03).

In another study of the American Cancer Society cohort, Jerrett et al. (2009a) used an ozone metric of the average from April to September of the daily maximum 1-hour concentrations and found significant associations with respiratory mortality that were robust to inclusion of $\text{PM}_{2.5}$. This metric, in Europe at least, will be determined largely by hemispheric and/or global scale emissions, even though some cities, like Los Angeles in the Jerrett study in 1982, had annual average ozone levels of about $200 \mu\text{g}/\text{m}^3$ (100 ppb).

Smith KR et al. (2009) do not explicitly quote the exposure metric used for ozone, but refer to Krewski et al. (2009) and Jerrett et al. (2009b). The former (see above) used summer and annual average concentrations, while the latter used annual average ozone

concentrations. Smith KR et al. (2009) found associations between ozone and cardiopulmonary mortality to be robust to inclusion of sulfate in a two-pollutant model.

Zanobetti & Schwartz (2011) used a metric of mean ozone from May to September, and a mean of “Spring and Autumn”. Their findings suggest that long-term exposure to ozone elevates the risk of mortality in different subgroups of susceptible populations (those suffering from congestive heart failure, myocardial infarction, diabetes and chronic obstructive pulmonary disease).

The majority of the papers that reported associations with mortality used the American Cancer Society II cohort. Some analyses found associations with respiratory mortality and some with all-cause and cardiopulmonary mortality. However, the Zanobetti & Schwartz (2011) study together with toxicological studies (see Question B1) provide further support for the effects of long-term exposures to ozone.

An issue that goes beyond the current WHO review, but is nonetheless relevant to policy responses, is that long-term average ozone concentrations represent the third most important greenhouse gas. Recent studies (Shindell et al., 2012; Anenberg et al., 2012) have shown that reductions in global ozone levels would have important benefits for human health and would also slow the rate of global temperature increase and improve food security (ozone is a potent agent for crop and vegetation damage). The study of the impact of ozone on human health globally used the concentration–response relationship derived from Jerrett et al. (2009a).

There is, therefore, a case for WHO to consider developing a guideline for long-term ozone exposures. There is stronger evidence linking health effects with summer, rather than annual, average ozone concentrations, so that a guideline could relate to 6-month summer averages.

Similarly, it would be helpful to determine the extent to which current or foreseen policies within the EU, or the UNECE CLRTAP Gothenburg Protocol (which covers a wider geographical area), are sufficient to reduce annual or 6-month summer average ozone concentrations. Depending on the outcome of this analysis, a logical next step would be engagement with other major emitters in the northern hemisphere, or globally, to consider possible actions to reduce these longer-term ozone concentrations – in particular, for methane, possibly using the CLRTAP Task Force on Hemispheric Transport of Air Pollution (co-chaired by the EU and the United States) to provide scientific evidence and to guide the discussions.. Some of the relevant countries are already parties to the CLRTAP, and this may offer some scope for initial discussions, but others, notably China and India, are not, and a different route may need to be found. In considering the implications of this analysis for its own policies, the EU should note that methane reductions – both within and outside the EU – are likely to be the most important in reducing long-term ozone concentrations.

Threshold for effects?

The response to this issue, under Question B2, concluded that the evidence for a threshold for effects from short-term exposures to ozone was inconsistent and that there was insufficient evidence to make a statement about a threshold for long-term exposures. For *short-term* effects, some evidence suggests a threshold in the range of 20–90 $\mu\text{g}/\text{m}^3$ for the hourly average ozone concentration. The conclusion of the answer to Question B2 was that where a threshold is observed, it is likely to lie below 90 $\mu\text{g}/\text{m}^3$ for the maximum hourly average. In the context of policy, the existence (or otherwise) of a threshold determines the health impact of a pollutant. In recommending metrics for health impact analyses of short-term exposures, this review (in answer to Question B3) recommends using SOMO35 and SOMO10. The SOMO35 metric was first suggested for use in health impact assessments by the Joint WHO/CLRTAP Task Force on Health (Amann et al., 2008). (Note that the definition of SOMO35 in that report contains a misprint of 35 ppm as opposed to 35 ppb). The SOMO10 metric, since it aggregates daily maximum 8-hour ozone concentrations above 10 ppb over a year, or 6 months, will probably be influenced by emissions from outside the EU, as well as those within the EU; the SOMO35 metric will do so to a lesser extent. As noted in the previous section, it is useful to clarify the extent to which currently foreseen policies will reduce SOMO35 and SOMO10 in the EU and the extent to which further emission reductions within and outside this region would be needed to reduce the impacts to acceptable levels.

The Answer to Question B3 also recommended carrying out a health impact assessment on long-term ozone concentrations as a sensitivity study, involving summer (6-month warm season) averages of daily maximum 1-hour concentrations, with cut-offs at 35 ppb and 55 ppb.

3. NO₂

The two main policy-related issues connected with NO₂ are: first, the question of causality and the potential confounding of the associations found in epidemiological studies by other pollutants (notably metrics of particle concentrations), which are often strongly correlated with NO₂; and second, the value of the annual limit value and/or air quality guideline and the strength of the evidence supporting it.

Both issues were addressed in the 2005 global update of the WHO air quality guidelines. For the question about causality, the report stated:

... since nitrogen dioxide is an important constituent of combustion-generated air pollution and is highly correlated with other primary and secondary combustion products, it is unclear to what extent the health effects observed in epidemiological studies are attributable to nitrogen dioxide itself or to other correlated pollutants.

The chamber study exposure results are clearly unequivocal on the causality question, and these provide much of the evidence in support of the hourly guideline and limit value.

Since the earlier report, however, more evidence for associations between adverse effects on health and NO₂ per se has emerged. Quoting the Answer to Question C2,

Many studies, not previously considered or published since 2004, have documented associations between day-to-day variations in NO₂ concentration and variations in mortality, hospital admissions and respiratory symptoms. Also, more studies have now been published showing associations between long-term exposure to NO₂ and mortality and morbidity. ... Chamber and toxicological evidence provides some mechanistic support for a causal interpretation of the respiratory effects.

The Answer goes on to note, regarding *short-term* effects, that, “As there is consistent short-term epidemiological evidence and some mechanistic support for causality, ... it is reasonable to infer that NO₂ has some direct effects”.

With regard to the question about *long term* effects, Question C2 notes that correlations with other pollutants are often high, but also notes that, “some epidemiological studies do suggest associations of long-term NO₂ exposures with respiratory and cardiovascular mortality and with children’s respiratory symptoms and lung function that were independent of PM mass metrics”. The Answer to Question C2, on long-term effects concludes, “As with the short-term effects, NO₂ in these studies may represent other constituents. Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations are suggestive of a causal relationship.”

Regarding the value of the long-term (annual) guideline on which the EU limit value is based, the 2005 global update of the WHO air quality guidelines noted that some population studies showed adverse effects “even when the annual average NO₂ concentration complied with the WHO annual guideline”. It also noted that, “some indoor studies suggest effects on respiratory symptoms among infants at levels below the guideline”. The report cited these conclusions as showing support for a lowering of the guideline value. However, it concluded that there was insufficient evidence to change the guideline limit value of 40 µg/m³.

The present review, however, in Question C2, presents further epidemiological evidence for associations between long-term outdoor exposures to NO₂ and adverse effects. This is a further advance on the evidence on which the guideline was originally based (indoor studies on respiratory symptoms using passive samplers for NO₂ measurement in some studies or qualitative exposure measures in others). Furthermore, the discussion in the previous paragraphs has noted the strength of these epidemiological associations. The Answer to Question C2 notes that both short- and long-term studies have found these associations at concentrations that were at or below the current limit values, which for NO₂ are equivalent to the WHO air quality guidelines.

Taken together with the strengthened case for causality of the epidemiological associations and the existing toxicological evidence, these conclusions indicate that there is no *health-based* case for either increasing or removing the NO₂ limit values in the EU

Ambient Air Quality Directive. There is a case for WHO to revise its current guidelines and to consider a short-term guideline based on epidemiological studies and a long-term guideline based on the outdoor, as opposed to the indoor, epidemiology. Depending on the outcome of this process, there could then also be a case for the EU to consider revising the Directive limit values.

4. SO₂

Controlled studies with exercising asthmatics indicate that some of them experience changes in pulmonary function and respiratory symptoms after periods of exposure as short as 10 minutes. Because exposure to sharp peaks depends on the nature of local sources and meteorological conditions, no single factor can be applied to this value to estimate corresponding guideline values over somewhat longer periods, such as an hour.

Day-to-day changes in mortality, morbidity or lung function related to 24-hour average concentrations of SO₂ are necessarily based on epidemiological studies in which people are, in general, exposed to a mixture of pollutants, with often little basis for separating the contributions of each to the effects. This is why guideline values for SO₂ were linked in earlier times with corresponding values for PM. Recent evidence, beginning with the Hong Kong study (Hedley et al., 2002) of a major reduction in sulfur content in fuels over a very short period of time, shows an associated substantial reduction in health effects (childhood respiratory disease and all-age mortality outcomes). More recently, the APHEKOM Project studied the effects of EU legislation to reduce the sulfur content of fuels in 20 European cities, finding a non-negligible reduction in ambient SO₂ levels and the resulting prevention of some thousand premature deaths. Nevertheless, there is still considerable uncertainty as to whether SO₂ is the pollutant responsible for the observed adverse effects or, rather, a surrogate for ultrafine particles or some other correlated substance. Based on several considerations – such as uncertainty of causality, uncertainty about no-effect levels and assuming that reduction in exposure to a causal and correlated substance is achieved by reduction of SO₂ concentrations – a guideline for a 24-hour mean was recommended as a prudent precautionary level.

Since the 2005 global update of the WHO air quality guidelines, some new studies on toxicological and health effects of SO₂ have been published. A reanalysis of the previous chamber study literature suggests a need to consider whether to increase the safety factor for the 10-minute guideline. For the 24-hour average guideline, the new studies show no obvious change in the size of the concentration–response function. As the lower end was already very low in previous studies, even quite marked changes in the size of the concentration response–function would have no effect on a guideline set on this basis (Answer to Question C7). However, the evidence should be looked at again.

Question D2

What evidence is available directly assessing health benefits from reducing air pollution?

Answer

There is reasonably consistent evidence from past and more recent studies that decreased air pollution levels, following an intervention or unplanned decrement in pollution, have been associated with improvements in health. The assessed decrements in pollution were not exclusively associated with legislation, but may have been due to strikes, German reunification and so on. In addition, there is significant and consistent evidence from around the world that workplace or public space smoking bans have resulted in a reduction in the cardiovascular health burden of the general population in the regions where they were introduced.

These findings are supported by a large body of remarkably coherent evidence from studies of both long- and short-term exposure to air pollution. The scientific work relies on naturally occurring exposure variability and provides effect estimates for quantifying health improvements that could be expected from long- or short-term reductions in air pollution exposures in a given population.

Rationale

The text below sets out collated and reviewed scientific evidence, including (but not limited to) studies published from 2005 onwards.

Intervention/accountability studies

The work presented here provides an overview of the most relevant, published intervention and/or accountability studies that assessed the health impact of changes in air quality. Many of these interventions are regulatory actions at the national, regional or local level that were specifically aimed at improving air quality; others are not interventions in the pure sense of the word, but may be unplanned side-effects attributable to political, economic or other societal changes that have led to substantial air quality changes (Henschel et al., 2012). These are sometimes called “natural experiments”. However, in some cases, it is difficult to definitively ascribe the benefits to the intervention because changes in air quality are multifaceted and may not exclusively be associated with the intervention under evaluation. This document includes both studies that have measured actual health outcomes and studies that estimated possible health outcomes, with an emphasis on the former.

Regulatory actions to improve air quality

National scale regulations

European air emission policies

Over the past few decades, the EU has implemented a number of legislative measures designed to improve air quality, by tackling emissions from various sectors. An assessment of the impact of a number of these policies, compared with a non-policy scenario, estimated that, with respect to road transport directives, significant reductions in emissions occurred – especially for carbon monoxide (-80%), non-methane volatile organic compounds (-68%), nitrogen oxides (-40%) and PM_{2.5} (-60%) – while over the same time period energy consumption in that sector increased by 20% (EEA, 2011). Inconsistent patterns were observed for ozone concentrations, with decreases in most areas, but with increases in Germany, the Netherlands and the United Kingdom. Overall, these policies have been effective in reducing air pollution; based on the observed pollution reductions, a European Environment Agency report predicted that the health impact of the road transport sector (in terms of years of life lost) was 13% and 17% for PM_{2.5} and ozone, respectively; this is based on averaging across all European Environment Agency member countries, compared with the non-policy scenario (EEA, 2011; Henschel et al., 2012).

Supporting evidence of health benefits associated with general air quality improvements was reported in Switzerland in the SAPALDIA study (Downs et al., 2007; Schindler et al., 2009). Between 1991 and 2002 a decrease of 5–6 µg/m³ in annual average PM₁₀ concentrations was observed. Downs et al. (2007) reported a reduction in the annual rate of decline in lung function in adult participants in 2002, compared with the change in lung function for 1991. Subsequently, Schindler et al. (2009) estimated in the same cohort the following health benefits that could be attributed to the observed PM₁₀ decrease: of 10 000 people, there were 259 fewer people with regular cough, 179 fewer people with chronic cough or phlegm, and 137 fewer people with wheezing and breathlessness in 2002 than in 1991. The authors concluded that reductions in particle levels in Switzerland over the 11-year follow-up period had a beneficial effect on respiratory symptoms among adults.

United States Clean Air Act and related air pollution control policies

National air pollution control policies in the United States have provided opportunities to evaluate the efficacy of these efforts regarding improved health. As originally designed, the Harvard Six Cities (cohort) Study (Dockery et al., 1993) was intended to be a prospective study of differential changes in air pollution across six cities in the United States due to the implementation of the United States Clean Air Act, its amendments, and related national ambient air quality standards. Differential changes in air pollution across the six cities did eventually occur, although it is difficult to attribute these directly to the Clean Air Act and enforcement of air quality standards, due to the complexity of implementing multiple regulations targeted at six key pollutants at the national and state levels and the long time frame over which the changes took place. Extended analyses of

the Harvard Six-Cities cohort (Laden et al., 2006; Schwartz et al., 2008) indicate that reductions in air pollution resulted in substantive declines in mortality risk.

The United States Clean Air Act, its amendments, and related public policy efforts to improve air quality also provided opportunities to evaluate if metropolitan areas with the largest improvements in air quality also had bigger improvements in health measured by life expectancy. Evaluating the time period between 1980 and 2000, it has been reported that greater reductions in air pollution were associated with greater increases in life expectancy, even after controlling for socioeconomic, demographic, and smoking variables (Pope, Ezzati & Dockery, 2009). Similar subsequent analysis of life expectancies for 545 counties in the United States for the period 2000–2007 found that further reductions in air pollution were associated with continued improvements in life expectancy (Correia et al., 2013). These studies all provide important evidence that improved air quality is associated with improved public health, but it remains difficult to attribute the air quality improvements directly to specific national-scale regulations.

Similarly, recent research by Lin et al. (2013) on the effect of the NO_x Budget Trading Program to improve regional air quality in the Eastern United States has found that ozone levels were decreased by 2–9% in New York State during the period 2004–2006. This resulted in fewer hospital admissions for respiratory disease (up to 11% lower in some counties, including the New York City metropolitan area), although some other counties showed an increase of nearly 18%. Ozone reductions as well as hospital admission reductions were reported to be greatest in late summer.

A recently published study directly evaluated air quality improvements related to the ability of the Clean Air Act Amendments of 1990 to reduce power plant emissions of sulfur oxides and nitrogen oxides. Morgenstern et al. (2012) tracked emission inventories and regional pollutant levels and used statistical methods to relate them to each other at different distances from the individual power generating sources. The study confirmed that there were PM_{2.5} reductions on the order of 1.07 µg/m³ (annual average) during the study period (1999–2005) that could be confidently linked to emission reductions under the Clean Air Act Amendments. The study did not assess health outcomes.

Miscellaneous air quality regulations in other countries

Additional evidence is provided in a few studies conducted in other countries. For example, Yorifuji et al. (2011) examined rules to curb diesel emissions in Tokyo, Japan, during the period 2006–2008. Concentrations of air pollutants gradually decreased during the study period: NO₂ decreased from 36.3 ppb to 32.1 ppb, and PM_{2.5} decreased from 22.8 µg/m³ to 20.3 µg/m³. These decreases in pollutant concentrations were tentatively associated with decreased rates of cerebrovascular mortality.

Foster & Kumar (2011) studied the health effects of air quality regulations in Delhi, which adopted radical measures to improve air quality, including, for example, the conversion of all commercial vehicles to compressed natural gas and the closure of polluting industries in residential areas from 2000 to 2002. They reported that the

interventions were associated with a significant improvement in respiratory health and that the effects were strongest among individuals spending a disproportionate share of their time outdoors.

Changes in fuel for domestic heating and transport

The reduction of the sulfur content of fuel in Hong Kong, 1990

Wong et al. (2012) conducted an extended analysis–assessment of the reduction of the sulfur content of fuel in Hong Kong in 1990, initially assessed by Hedley et al. (2002). They evaluated the effects of subsequent regulations on mortality and life expectancy and conducted an additional assessment of long-term benefits of improved air quality over a 20-year period that included NO₂, SO₂, ozone, PM₁₀ and PM composition. A decrease in NO₂, SO₂ and several PM components, of which nickel and vanadium were the most consistent, was observed. However, after the intervention, no consistent change in PM₁₀ concentration was reported. Associations between NO₂, SO₂, PM and PM-associated metals and mortality were reported (Wong et al., 2012). Although it was not possible to definitively link changes in specific PM components to changes in mortality (comparing pre- and post-ban study periods) due to data limitations, the follow-on study did not, however, appear to rebut the original findings that there was an association between PM level and mortality and that an improvement was observed after the ban. An early study of the intervention noted a positive effect on children’s respiratory health (Peters et al., 1996).

The Irish coal sale bans, 1990–1998

Clancy et al. (2002) reported that the ban on the sale of coal in Dublin in 1990 led to a 71% drop in black smoke levels and a 34% drop in SO₂ levels and that this was associated with decreases in total (7%), cardiovascular (13%) and respiratory (8%) mortality. Due to the success of the Dublin coal ban, the ban was extended in a stepwise manner to other Irish cities during 1995 and 1998 and resulted in significant reductions in particulate pollution levels; no clear trend, however, was reported for SO₂ (Goodman P et al. 2009). In a recent reanalysis of the data, Dockery et al. (2013) examined the health effects associated with the initial Dublin ban and with the various stepwise implementations of the ban in other cities. They reported that these bans were associated with reductions in cardiovascular hospital admissions and reductions in respiratory mortality and hospital admissions, confirming the earlier published analyses for Dublin alone. However, the improvements in cardiovascular and total mortality originally reported in Dublin were not in evidence in Dublin or in other Irish cities after taking into account the general decreasing trend in cardiovascular mortality due to other factors (Dockery et al., 2013).

Change-out of wood stoves in a rural mountain community – Libby, Montana

Noonan et al. (2011) evaluated a programme to replace older, polluting wood stoves used for home heating with newer, more efficient models, to improve air quality in a rural community. They found that the change-out programme was effective in reducing ambient PM_{2.5} concentrations, but there was substantial variability in indoor

concentrations in the homes where they took detailed measurements before and after the wood stove replacement. Possible factors for this variability include stove operation and the presence of other indoor sources of particles. Children's respiratory health, as reported in surveys filled out by the parents, was somewhat improved, although there were no differences among children from homes where stoves were changed compared with homes with other types of heating.

Residential wood burning regulations in San Joaquin Valley, California, 2003

In November 2003 in San Joaquin Valley, California, which was classified by the EPA as a serious nonattainment area for the National Ambient Air Quality Standards (Hall, Brajer & Lurmann, 2008), a regulation banning residential wood burning in areas below 914.4 m (3000 ft) with natural gas, when forecasts predict poor air quality, was implemented to improve the seasonal poor air quality in wintertime. Lighthall, Nunes & Tyner (2009) conducted comparative case studies in the Bakersfield and Fresno/Clovis metropolitan areas. They reported that, in Fresno/Clovis, PM_{2.5} levels in the four post-rule winters (28.3–34.6 µg/m³) were reduced compared with three pre-rule winters (41.0–45.7 µg/m³). Modelling results indicated similar reductions compared with a non-ban scenario in both locations (Lighthall, Nunes & Tyner, 2009).

Gilbreath & Yap (2008) reported a 4.8% (95% CI: 1.00–1.09%) reduction in the risk of mortality due to ischaemic heart disease and a 5.4% (95% CI: 0.97–1.14) reduction in the risk due to cerebrovascular diseases after the intervention. In addition, Lighthall, Nunes & Tyner (2009) estimated that mean annual mortality costs saved by the intervention were in the range of US\$ 367.5–430.6 million in Fresno/Clovis and US\$189.1–239.9 million in Bakersfield; the range of saved morbidity costs was US\$11.0–26.6 million and \$5.7–14.1 million, respectively.

Change-out of wood stoves and environmental regulations in Tasmania, Australia, 2001

Johnston et al. (2013) described a wood heater replacement programme combined with community education campaigns and enforcement of environmental regulations, starting in 2001, to reduce ambient pollution from residential wood stoves in Launceston, Tasmania. They reported a decrease in mean daily wintertime concentrations of PM₁₀ from 44 µg/m³ during 1994–2000 to 27 µg/m³ during 2001–2007. The period of improved air quality was associated with small non-significant reductions in annual mortality (males and females combined). In males, the observed reductions in annual mortality were larger and significant for all-cause (11.4%), cardiovascular (17.9%), and respiratory (22.8%) mortality. In wintertime, reductions in cardiovascular (19.6%) and respiratory (27.9%) mortality were of borderline significance (males and females combined). There were no significant changes in mortality in the control city of Hobart.

Switch to natural gas use in transport and heating in Santiago, Chile, 2003

Mena-Carrasco et al. (2012) estimated reductions in PM_{2.5} emissions and subsequent health benefits from increased natural gas use in: (a) transport, replacing the diesel bus fleet; and (b) heating, replacing wood burning stoves, in Santiago, Chile, applying two

scenarios. Estimated annual reductions of PM_{2.5} of 0.33 µg/m³ and 2.07 µg/m³ were associated with 36 avoided premature deaths for the transport scenario, and 229 for the natural gas heating scenario, respectively.

Traffic-related initiatives

In this section, we describe several types of traffic-related interventions. First, we describe studies of low emission zones, which are now in effect in many cities in Europe. Second, we describe studies of congestion charging zones and other interventions, such as reduced speed limits and traffic bypasses that were not specifically designed to improve air quality, but may lead to air quality benefits and associated health benefits.

Low emission zones in Rome, Italy, 2006

Cesaroni et al. (2012) examined the effect of the low emission zones, implemented in two city areas in Rome, on traffic-related PM₁₀ and NO₂ concentrations and on mortality for subjects living near highly trafficked roads from 2001–2005. They reported improvements of air quality and a positive impact on the public health of residents living along busy roads, gaining 3.4 days per person (921 years of life gained per 100 000 population) due to reductions in NO₂ associated with the interventions. The number of years of life gained was higher in higher socioeconomic groups, compared with lower ones.

Low emission zones in the Netherlands, 2007

In 2007 and 2008, low emission zones went into effect in several cities in the Netherlands that restricted the access of older trucks to enter the inner city, based on compliance with increasingly strict European emission standards. Boogaard et al. (2012b) did not find substantial changes in pollutant concentrations associated with the low emission zones 2 years after they went into effect compared with before. One possible reason offered was that old trucks constitute only a small part of the fleet. Boogaard et al. did find that street and urban PM_{2.5} concentrations were reduced more during the study period than in suburban areas, but factors other than the traffic policies may have contributed.

The London congestion charging zone, 2003

On 17 February 2003, the traffic congestion charging zone was launched in London. Its main objective was to reduce traffic congestion in the city centre area covering about 22 km², by charging a fee for four-wheeled vehicles entering the zone Monday to Friday between 7 a.m. and 6 p.m. (TfL, 2007). In addition, further measures were taken to improve the traffic flow – for example, improvements of the bus network and of walking and cycling schemes. After one year, 30% less congestion was successfully achieved (TfL, 2004). The measure was not introduced specifically to reduce air pollution.

Tonne et al. (2010) investigated if there were any health benefits associated with the implementation of the congestion charging zone; they reported associations between changes in nitrogen oxides and cardiorespiratory hospital admissions from 2001 to 2004. They also reported a significant association for bronchiolitis admissions, adjusting for

spatial dependence at the borough level, but with significant spatial variation. In a separate analysis, in which they modelled the impact of the congestion charging zone traffic-related pollution on mortality, they estimated the years of life gained per 100 000 population, according to the modelled declines in NO₂, to be 26 years for Greater London, 183 years for congestion charging zone residents (a very small fraction of the London population), and only 18 years for remaining wards. Overall, these findings show a very modest impact of the congestion charging zone on traffic-related air pollution levels and public health.

In a separate analysis of actual measurements of background pollutant concentrations, it was found that introduction of the congestion charging zone was associated with significant increases in concentrations of nitric oxide and increases in NO₂ and ozone within the congestion charging zone relative to the non congestion charging zone part of the city. There was also some evidence of a reduction in PM₁₀ and carbon monoxide (Atkinson et al., 2009; Kelly et al., 2011). However, causal attribution of these changes to the congestion charging zone was considered inappropriate because the congestion charging zone had been introduced concurrently with other traffic interventions, such as traffic light and lane changes and the introduction of exhaust aftertreatment on diesel buses.

The Stockholm congestion charging trial, 2006

A congestion charging scheme trial was implemented in Stockholm on 3 January 2006, lasting until 31 July 2006 and covering the inner city centre of approximately 30 km² (Eliasson, 2008). Charges to enter were staggered and depended on the time of day, starting from 7:00 a.m. until 6.30 p.m., and they were arranged to be the highest during the rush hours. It was not introduced specifically to reduce air pollution. Simultaneously public transport was expanded and reinforced, allowing higher capacity and frequency (Eliasson et al., 2009). All primary objectives of the congestion charging scheme trial were met, particularly the effect on the magnitude of traffic flow across a cordon during charging hours, which stabilized at about 22% less traffic than in 2005 (Eliasson, 2008).

Johansson et al. (2009) reported reductions in air pollution levels in the inner city centre after comparing scenarios with and without the congestion charging scheme trial for 2006. The levels were reduced by 10.0% for nitrogen oxides, 7.6% for total PM₁₀ and 10% for the PM₁₀ fraction from vehicle exhausts. Taking nitrogen oxides as a marker of traffic emissions, a public health impact was calculated, assuming that the decrease of the exposure level persists, and yielded 206 years of life gained per 100 000 population for the area of Greater Stockholm over a 10-year period. These results are very similar to estimates of Tonne et al. (2008) for London.

The improvement due to the congestion charging scheme trial was perceived to be positive among the majority of the public and was affirmed by a referendum on a proposal to make the system permanent (Eliasson et al., 2009; Henschel et al., 2012). A recent study by Börjesson et al. (2012) showed that the air quality improvements have persisted since the scheme was made permanent in 2007.

Other evidence of lower traffic exposure and improved health outcomes

Consistent evidence has been reported that links living near major roads and/or traffic-related air pollution to adverse effects on health (Hoek et al., 2002b; WHO Regional Office for Europe, 2005; Salam, Islam & Gilliland, 2008; Gan et al., 2010; HEI Panel on the Health Effects of Traffic-Related Air Pollution, 2010). In addition, a positive health impact has been observed when moving from areas with high to areas with lower air pollution and traffic (Avol et al., 2001). There is ample evidence that certain traffic measures, indeed, lead to improved air quality; for example, reductions in traffic speed on a section of a busy highway in the Netherlands have been associated with improved air quality in areas adjacent to the highway (Keuken et al., 2010). In Wales, construction of a bypass to relieve nearby congested streets was shown to improve PM levels by about 28%. The authors reported that, “the bypass reduced pollutant levels to a degree that probably alleviates rhinitis and rhinoconjunctivitis but has little effect on lower respiratory symptoms” (Burr et al., 2004).

Temporary air-quality changes during major athletic events

Interventions affecting traffic and pollution sources during major events provide opportunities to evaluate the short-term health effects of air pollution. Where it is found that such events are statistically associated with changes in pollution concentrations and/or health events, any causal interpretation will need to take into account that these events disturb the normal equilibrium of city life in a variety of other ways, some of which could also explain changes in health events, such as emergency hospital admissions.

1996 Summer Olympic Games in Atlanta, Georgia

During the 1996 Atlanta Olympics, measures to reduce traffic congestion, while providing a functional transport network, were implemented. Friedman et al. (2001) reported improvements in air quality (particularly ozone concentrations) in Atlanta and an associated reduction in asthma emergency room visits and hospitalizations; however, more recently Peel et al. (2010) contradicted these findings, stating important potential confounders had not been addressed in the original study. For example, the ozone reductions were found to be regional in nature and thus could not be definitively attributed to the traffic measures; also, the 17-day period of the Olympic Games may have been too short to observe significant health benefits. It should also be kept in mind that the traffic measures were not intended to improve air quality, and it was difficult to show an improvement in traffic flow (Friedman et al., 2001; Peel et al., 2010).

2008 Summer Olympic Games in Beijing, China

In the lead up to the Beijing Olympics, there was growing concern about the very poor air quality and how it might affect competitors. This led to the Chinese authorities implementing a number of measures to reduce air pollution during the games, such as reduced traffic congestion, and measures to curb significant local sources, such as emissions from major factories and construction in Beijing and surrounding areas.

A number of prospective studies were designed to assess the changes in air quality and the health effects resulting from this. Improvements in air pollution levels were reported, comparing the pre-Olympic period with the Olympic period, though weather conditions during the Olympics were estimated to have contributed about 40% to this improvement (Wang et al., 2009; Wang et al., 2010).

Li Y et al. (2010) reported a significant reduction in adult outpatient visits for asthma during the Games, while Lin et al. (2011) found reductions in black carbon and exhaled nitric oxide, a biomarker of acute respiratory inflammation, in 36 schoolchildren. In addition, Hou et al. (2010) observed that human exposure to PM₁₀ and associated health economic costs were lowest during the Olympic period, compared with periods before and after. Huang et al. (2009) reported improvements of heart rate variability in 43 elderly residents, previously diagnosed with cardiovascular diseases. Similar results were presented by Wu S et al. (2010) who assessed heart rate variability in 11 young healthy taxi drivers.

In addition, a prospective panel study of healthy young adults and changes in air pollution associated with the Beijing Olympic Games was conducted. Rich et al. (2012a) and Zhang et al. (2013) reported that Olympics-related changes in air pollution in Beijing were associated with acute changes in biomarkers related to cardiovascular disease pathophysiological pathways (systemic inflammation and thrombosis, heart rate, and blood pressure). A subsequent analysis from this Beijing Olympic Games panel study reported that exhaled breath and urinary biomarkers of pulmonary and systemic oxidative stress and inflammation were also associated with air pollution (Huang et al., 2012). However, findings were of uncertain clinical significance. Another study by Jia et al. (2011) estimated a reduction of 46% in excess PAH-induced inhalation cancer risk due to improved air quality during the source-control period of the Olympics, based on-site pollutant measurements and unit risk estimates of WHO and the California Office of Environmental Health Hazard Assessment.

Asian Games in Korea, 2002

Lee et al. (2007a) conducted an intervention study of traffic restrictions during the 2002 Summer Asian Games in Busan, Korea. They reported that 14 consecutive days of traffic volume control in Busan during the 2002 Summer Asian Games reduced all regulated air pollutants by 1–25%. The estimated RR of hospitalization for asthma in children younger than 15 years during the post-Games period, compared with the baseline period, was 0.73 (95% CI: 0.49–1.11). The reduced RR observed in 2002 was distinctly different to RRs observed during the same time period in preceding and following years. For example, the RR in 2003 was 1.78 (95% CI: 1.27–2.48), indicating the observation in 2002 was not simply a seasonal effect.

Air quality improvements due to unplanned events

In several well-documented cases, *natural experiments*, such as strikes, factory closures, and economic recessions have resulted (temporarily) in significantly improved air quality, combined with worsened air quality after the intervention ended. Here we describe

studies that have estimated the health benefits associated with the unintended air quality changes. These studies provide further important evidence that improved air quality – however it was accomplished – leads to improved public health.

The nationwide copper smelter strike in the United States in the late 1960s

A nationwide copper smelter strike in the United States in 1967/1968 was associated with a marked drop in regional SO₂ and improved visibility (Trijonis, 1979). Pope, Rodermund & Gee (2007) reported a small, but statistically significant 1.5–4.0% decrease in mortality associated with the strike.

The Utah Valley steel mill closure, United States, 1986

A local steel mill in Utah Valley – being the largest single source of local air pollution, accounting for about 82% of industrial PM (PM₁₀) emissions – closed due to a strike in August 1986 for 13 months. Retrospective studies by Pope (1989, 1996) reported substantial reductions in concentrations of air pollution, with corresponding reductions in paediatric respiratory hospital admissions being associated with the mill closure. In addition, Pope (1996) and Parker, Mendola & Woodruff (2008) reported air pollution associations with lung function and respiratory symptoms, school absences, respiratory and cardiovascular mortality and preterm birth.

German reunification, 1990

The reunification of the former German Democratic Republic (East Germany) and the former Federal Republic of Germany (West Germany) in 1990 was accompanied by marked changes in the political environment and in the socioeconomic structures. Air quality improved markedly after the reunification, with air pollution levels in East Germany moving towards West German levels over time (Ebelt et al., 2001; Sugiri et al., 2006).

Peters et al. (2009) assessed the short-term impact of improved air quality on daily mortality in Erfurt from 1990 to 2000; they reported a delayed short-term association between daily mortality and NO₂, carbon monoxide, ultrafine particles, and ozone. They found that associations between pollution levels and mortality remained the same over the study period; given the clear reduction in pollution after the German reunification, the most likely conclusion is that the improvements in pollution did lead to some public health benefits overall. Peters et al. used a new time varying coefficients approach, which was meant to look at the question whether the change in pollution sources had changed the toxicity of the pollutant mixture. They were unable to show changes in time varying coefficients between the beginning and the end of the study period. This would seem to indicate that the toxicity of the mixture did not change over time, even though the sources changed from combustion of brown coal to that of natural gas, combined with a relative increase in the contribution of traffic sources. The study should be taken as an exploration of methods. Overall pollution levels went down; given the consistent associations with mortality, one may conclude (even though not explicitly stated by the authors) that there

was likely to be an improvement in public health as well. These results corroborated the results from a study by Breitner et al. (2009).

In addition, Sugiri et al. (2006) reported that in 1991 6-year-olds in East Germany had a worse lung function than children in West Germany and that by 1997 the difference in lung function vanished simultaneously with the difference in total suspended PM concentrations. A negative effect of exposure to traffic-related pollution and lung function was noted. These results are consistent with findings of earlier studies (Krämer et al., 1999; Heinrich et al., 2000; Frye et al., 2003).

Improved air quality during economic recessions

Some studies have evaluated the effect of economic recessions on air quality. Early studies of the economic downturns in the 1970s and 1980s showed significant air pollution reductions during that time, which were estimated to have led to significant mortality benefits in adults (Brown et al., 1975) and infants (Chay & Greenstone, 2003). More recently, a study in Europe showed that a combination of environmental policy and economic recession in the 1990s led to reductions in the levels of nitrogen oxides (Castellanos & Boersma, 2012); another study, by Davis (2012), also assessed the respective roles of air quality regulations and economic factors in improving air quality.

Question D4

The 6th Environment Action Programme aims to “achieve levels of air quality that do not give rise to significant negative impacts on and risks to human health and the environment (Article 7 (1) of Decision No. 1600/2002/EC). Is there evidence of a threshold in the concentration–response curves for PM_{2.5}, ozone and NO₂?

Answer

Existing studies do not provide evidence of a threshold in the concentration–response curve between PM_{2.5} and health outcomes, either for short- or long-term exposures at the commonly observed ambient levels. On the contrary, for long-term exposures, there is some evidence that the curve increases more rapidly at lower concentrations than at higher concentrations. Enhanced methodologies are proposed to better account for the uncertainty incorporated in epidemiological designs, especially in the investigation of long-term effects and outside the range of exposures observed in cohort studies. Similarly, there is lack of evidence of a threshold for NO₂ and ozone, although the evidence base for assessing the existence of a threshold or the shape of the concentration–response curve is weaker than for PM_{2.5}.

Rationale

Short-term exposures

Results from the epidemiological studies that investigated the shape of the concentration–response associations between PM_{2.5} exposure and short-term health effects, either on mortality or morbidity, conclude that there is no evidence for departure from linearity or the presence of a threshold. This conclusion is derived mainly from multicity studies that have sufficient power for such an investigation, while only a single-city report indicated the presence of a threshold at levels of about 20 µg/m³.

Most epidemiological studies that investigated the concentration–response association between short-term health effects and particles focused on PM₁₀, and recently on PM_{2.5}, as measurements became available. In accordance with the Answer to Question A5, multicity studies from 30 European cities (Katsouyanni et al., 2009) and 4 Asian cities (Wong et al., 2010b) found no evidence for deviation from linearity or the presence of a threshold for PM₁₀ associations. Results from multicity analyses that focused on PM_{2.5} in 10 metropolitan areas in the European Mediterranean region (Samoli et al., 2013; Stafoggia et al., 2013) and in 6 cities in the United States (Schwartz, Laden & Zanobetti, 2002) replicated these findings, either for associations with mortality (Samoli et al., 2013; Schwartz, Laden & Zanobetti, 2002) or morbidity (Stafoggia et al., 2013), especially within the common range of PM_{2.5} observed between cities included in the analyses, usually between 10 µg/m³ and 35 µg/m³. Due to less information at the extremes of the PM distribution, the power to sufficiently detect the shape outside this range is limited. Nevertheless, there is evidence of a logarithmic shape with steeper slopes in the lower

ranges – below 30–35 $\mu\text{g}/\text{m}^3$ and mostly for mortality outcomes – but there is insufficient power in the study designs to properly identify it.

Results obtained from single-city analyses are contradictory; for the association between all-cause mortality and $\text{PM}_{2.5}$, Peters et al. (2009) found no evidence for a departure from linearity in Erfurt, Germany, while Smith et al. (2000) reported a possible threshold in Phoenix, Arizona, of about 20 $\mu\text{g}/\text{m}^3$. Simulations in the context of the APHENA study (Katsouyanni et al., 2009), though, have shown the limited ability of single-city analysis to capture possible thresholds in a concentration–response investigation. Cause-specific associations or effects in susceptible groups may present different patterns (exacerbation at certain levels with subsequent adaptation and flattening of the curve), but these are not detectable through existing epidemiological designs and applied methodologies. Since most research has focused on such broad health outcomes of large population groups as total mortality outcomes or hospital admissions among the elderly, the associations detected may not represent the curves for groups of specific interest, such as children; instead, the linear curve may be seen as a composition of postulated *partial* curves among population groups with different sensitivities to PM exposure and may be used effectively for the protection of the whole population.

The concentration–response function for the association between ozone exposure and adverse short-term effects on health has been studied less than that for particles. Results from multicity studies on the shape of the association between ozone exposure and mortality outcomes do not support the assumption of a threshold and indicate linear associations – mostly in the range between 30 $\mu\text{g}/\text{m}^3$ and about 120 $\mu\text{g}/\text{m}^3$, where there is sufficient information (Bell, Peng & Dominici, 2006; Gryparis et al., 2004; Katsouyanni et al., 2009). There is evidence of effects even at low levels that seems hard to reconcile with chamber study results, which nevertheless look at relatively healthy subjects for a short time. Smith, Xu & Switzer (2009), in a reassessment of the evidence for the United States, reported larger effects in higher ranges. The curves reported usually correspond to annual effects, but due to the importance of seasonal adjustment in the investigation of the short-term effects of ozone, research should report season-specific curves. Along these lines, Atkinson et al. (2012b) reported a possible threshold in the relationship of daily ozone with total mortality for both four urban (including London) and four rural areas in the United Kingdom during summer months only, although the threshold models did not have a statistically significant better fit than the ones that assumed a linear association. Future research needs to replicate such analyses and (furthermore) – due to the inconsistent evidence (between areas) of confounding of the short-term effects of ozone by particles (Katsouyanni et al., 2009; Anderson et al., 2012) – to focus on concentration–response functions after considering possible confounders.

In accordance with the Answer to Question C4, the concentration–response association between NO_2 and short-term health effects should be optimally derived after controlling for particles, especially $\text{PM}_{2.5}$, due to the strong correlation between the two pollutants and the unresolved contribution of each one to the observed adverse effects on health and the insufficient evidence to date as to the causal role of NO_2 for the effects observed. Concentration–response curves reported so far – mainly from multicity studies, although

they did not consider such an adjustment – indicate no deviation from linearity in the commonly observed concentration ranges. Evidence on the concentration–response association between NO₂ and short-term health effects has come mainly from multicity studies (Samoli et al., 2003; Chen et al., 2012b) that found no deviation from linearity for the association with all-cause mortality – which is in accordance with the sparse results coming from single-city studies (Peters et al., 2009). A recent review of controlled exposure studies on the effects of NO₂ on asthmatics found no evidence of effects at very high levels, which may reflect patterns of response different from those considered or may reflect a logarithmic shape at higher concentrations (Goodman J et al., 2009).

Long-term exposures

The shape of the association between long-term exposure to ambient PM_{2.5} and mortality has been examined in a number of cohort and cross-sectional studies. A singular form of the concentration–response curve has not been clearly identified, nor has a threshold been clearly observed. Consequently, the simplest form of curve, linear, has usually been preferred, based on statistical inference criteria when such an examination has been conducted. However, some evidence suggests that for cardiovascular mortality, the curve increases more rapidly at lower than at higher concentrations. Functional forms that have this characteristic may be better suited to predict PM_{2.5}-related mortality risk than a linear model. RR estimates based on these forms are highly sensitive to the baseline comparison concentration, and thus a positive counterfactual level should be used when evaluating RR estimates for burden assessment and cost–benefit analysis – that is, a de facto threshold.

Population epidemiology studies of mortality and long-term exposure to ambient PM_{2.5} have not specifically attempted to estimate a concentration below which there is no evidence of an association. Indirect evidence is available from studies with low mean concentrations or plots of natural spline curves. An assessment of these studies is given in Question A5. However, the specific concordance between the strength of evidence of a threshold and such assessments is not known. It is likely that these studies suggest that a threshold, if it exists, is well below the mean study concentrations.

There is some evidence that the shape of the cardiovascular mortality association with long-term exposure to ambient PM_{2.5} is supralinear (Krewski et al., 2009; Crouse et al., 2012; Lepeule et al., 2012), with the risk increasing more rapidly for lower concentrations. A similar supralinear association was observed by Pope et al. (2011) when comparing PM_{2.5}–cardiovascular mortality risks between outdoor air, second-hand smoke, and active smoking exposures. However, such supralinear risk functions are highly dependent on the baseline concentrations against which the RR is evaluated.

The EPA used RR estimates from a single cohort study (by the American Cancer Society) in their risk assessment and benefit analysis (EPA, 2010a). They assumed a threshold of risk at the lowest measured concentration of PM_{2.5} in the American Cancer Society study, 5.8 µg/m³. They assumed the risk function was of the form: $\exp\{\beta(PM_{2.5} - 5.8)\}$ throughout the concentration range observed in the United States. They also considered

an RR model of the logarithm of concentration of the form:

$$\exp\{\gamma \log(PM_{2.5})\} / \exp\{\gamma \log(5.8)\} = \left(\frac{PM_{2.5}}{5.8}\right)^\gamma$$
, which has diminishing incremental increases in RR as concentration increases, when γ is less than 1. Estimates of both β and γ were obtained from Krewski et al. (2009). The uncertainty in these parameter estimates was based on a single cohort study and determined by sampling uncertainty. The heterogeneity of risk among other cohort studies was not incorporated into their uncertainty characterization.

There are a few points that need to be made when considering the use of a linear risk function.

1. Assuming the concentration–response function extends down to 0 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ is an extrapolation beyond the observed data, since no cohort study used exposure concentrations that low. The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) took a very strict approach to evidence that assumed knowledge of the shape of the function for which there were observations, and the EPA (2010) assumed no health benefits were below 5.8 $\mu\text{g}/\text{m}^3$.
2. Reliable estimates of risk from any study can only be made in the 5th to 95th percentile of exposure, since identifying the shape in the lower and upper 5th percentiles is almost impossible. The 95th percentile of most United States cohort studies is below 20 $\mu\text{g}/\text{m}^3$. So assuming a linear concentration–response curve above 20 $\mu\text{g}/\text{m}^3$ is again making a decision without direct empirical evidence. For Europe, although most ambient $\text{PM}_{2.5}$ concentrations are below 20 $\mu\text{g}/\text{m}^3$, some (particularly in eastern Europe) are not, and thus extrapolation of the empirical evidence is required. We do have some indirect evidence from a Chinese cohort (Cao et al., 2011) that suggests that changes in cardiovascular mortality risk at $\text{PM}_{2.5}$ concentrations ranging from 40 $\mu\text{g}/\text{m}^3$ to 160 $\mu\text{g}/\text{m}^3$ are much lower than United States cohort studies suggest. Therefore, it is problematic to assume a linear concentration–response function throughout the concentration range of interest in Europe.
3. There are some challenges in characterizing uncertainty in the linear risk model. Selecting a single study and using the sampling uncertainty from that study likely underestimates the true uncertainty in risk, since the risk estimate from a single study is unlikely to fully represent the true risk. Estimating uncertainty based on multiple cohort studies can lead to a highly dispersed uncertainty distribution with potentially negative support – for example, see the large variation in RR estimates among eight cohort studies for ischaemic heart disease mortality in Fig. 1 below. To strengthen their estimates, The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) borrowed additional information on $\text{PM}_{2.5}$ -related mortality risk from other sources of exposure at much higher concentrations. The resulting uncertainty intervals did not include zero in the four causes of death examined (see Fig. 1).
4. There is some concern that the risk estimates from cohort studies of ambient air pollution are unrealistically large compared with other $\text{PM}_{2.5}$ -related exposures. For

example, the hazard ratio for ischaemic heart disease mortality from the American Cancer Society for a change of $10 \mu\text{g}/\text{m}^3$ is 1.29 (Krewski et al., 2009). The RR of smoking 1–3 cigarettes a day is 1.61 (Pope et al., 2011). A change in ambient $\text{PM}_{2.5}$ concentration of $18.7 \mu\text{g}/\text{m}^3$ is associated with a hazard ratio of 1.61. The American Cancer Society risk estimate is moderate in the distribution of ischaemic heart disease mortality risk estimates. Such a contrast in pollution is well within the $\text{PM}_{2.5}$ distribution in Europe and makes a striking statement about the toxicity of fine particle mass. Incorporating risk information from other $\text{PM}_{2.5}$ sources into an integrated model does provide additional strength to estimates of risk within the lower part of the distribution of global ambient concentrations currently observed in Europe.

The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) suggests that a positive counterfactual concentration be used for burden analysis when supralinear RR functions are employed. Their counterfactual concentration is bounded by the minimum concentrations observed in the studies used to estimate risk and by some low percentile of the $\text{PM}_{2.5}$ distribution. There is clearly no evidence of an association below the levels observed, and it is impractical to estimate the shape of the curve at the extremes of the exposure distribution. The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) suggests that the 5th percentile be used and that the lower and upper bounds on the counterfactual concentration be determined by the corresponding minimum and 5th percentile, respectively, of the American Cancer Society Cancer Prevention cohort (Krewski et al., 2009), the largest cohort study of air pollution. The minimum was $5.8 \mu\text{g}/\text{m}^3$ and the 5th percentile was $8.8 \mu\text{g}/\text{m}^3$. The midpoint of this range is $7.3 \mu\text{g}/\text{m}^3$.

The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) also postulated a flexible RR function of the form:

$$RR_{IER}(x) = \begin{cases} 1, & x < x_{cf} \\ 1 + \alpha(1 - e^{-\beta(x-x_{cf})^\rho}), & x \geq x_{cf} \end{cases} \quad (1)$$

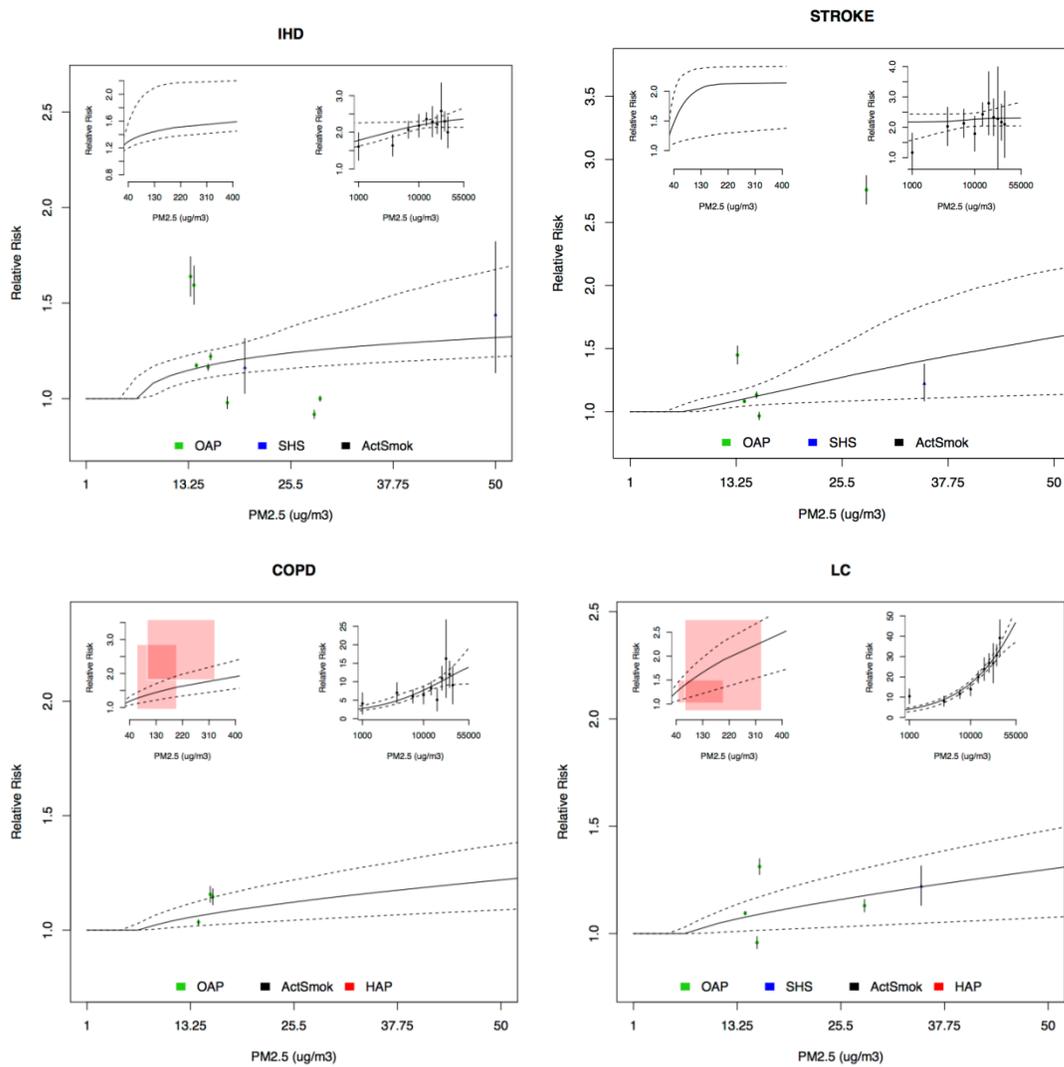
This integrated exposure–response RR function is characterized by four unknown parameters $(\alpha, \beta, \rho, x_{cf})$, with x_{cf} the $\text{PM}_{2.5}$ counterfactual concentration below which no association is assumed. The parameters (α, β, ρ) are estimated using curve fitting methods in which observations are drawn from RR estimates of outdoor air pollution studies, studies of second-hand smoke, studies of the burning of biomass for household heating and cooking, and studies of active smoking, represented by RRs associated with specific cigarettes-per-day categories. Study-specific RR estimates are evaluated at their respective $\text{PM}_{2.5}$ mean concentrations minus the counterfactual concentration for outdoor air pollution studies. Equivalent ambient $\text{PM}_{2.5}$ concentrations are assigned to second-hand smoke and active smoking studies by the methods reported by Pope et al. (2011).

Uncertainty in the RR function is characterized by the uncertainty in each study-specific RR estimate, using simulation methods. Uncertainty in the counterfactual concentration is modelled as a uniform distribution between the minimum and 5th percentile. Weighted non-linear curve fitting methods are used in which each RR estimate is weighted by the

inverse of the variance of the estimate, thus giving more importance to studies with greater precision. This approach also borrows strength among studies of several sources of PM_{2.5} exposure in estimating the uncertainty in the risk function, since there are few cohort studies of ambient air pollution.

The Global Burden of Disease Study 2010 (Lim et al., 2012; Burnett et al., under review) examined four common causes of death: ischaemic heart disease, stroke, chronic obstructive lung disease and lung cancer. Summary results are presented in Fig. 1. The supralinear nature of the curve is clearly evident for each cause of death.

Fig. 1. RRs for four causes of death examined^a



COPD: chronic obstructive pulmonary disease; IHD: ischaemic heart disease; LC: lung cancer; solid line: predicted values of the integrated exposure–response model; dashed line: 95% CI; OAP: outdoor air pollution; ActSmok: active smoking; HAP: household air pollution.

^a In Fig. 1, the predicted values of the integrated exposure–response model are represented by solid lines and the 95% CIs by dashed lines for ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD) and lung cancer (LC) mortality. Source-specific RRs (points) and 95% CIs (error bars) are also presented. The left-hand insert graph represents the household air pollution (HAP) concentration range.

The shaded boxes for COPD and LC mortality represent uncertainty (height) and exposure contrast (width) of RR HAP estimates. The right-hand insert graph depicts active smoking concentration range.

There is evidence that ozone is related to respiratory mortality, but the specific role it plays in contributing to cardiovascular mortality has not been clearly distinguished from that of PM_{2.5}. A threshold for the effect of ozone on respiratory mortality is plausible, but the statistical evidence to identify a specific threshold concentration is limited.

The evidence for an association between long-term exposure to ground level ozone and mortality is reviewed in Question B1 and that for the existence of a threshold in Question B2. Although several cohort studies observe a positive association of ozone with all-cause and cardiovascular mortality, they are often confounded by PM_{2.5} – so much so that it is difficult to precisely estimate the magnitude of the association. Consequently, it is difficult to determine either if a threshold exists or the shape of the concentration–response function. An independent association between long-term exposure to ozone and respiratory mortality was observed in the American Cancer Society Cancer Prevention II cohort, after controlling for PM_{2.5} (Jerrett et al., 2009a). Evidence for a threshold was detected ($P = 0.06$). The estimate of the threshold was 56 ppb, based on summertime 1-hour daily maximum concentrations with a 95% CI of 0–60 ppb. The estimate of the linear portion of the threshold model was 0.0039 per ppb, with a standard error of 0.0011 per ppb.

The evidence for an association between long-term concentrations of NO₂ and mortality is reviewed in Question C2. There is a growing body of evidence to support an independent association between long-term exposure to NO₂ and mortality that is not completely attributable to fine PM. However, enough evidence does not exist to identify the shape of the mortality–NO₂ response function and whether a threshold exists.

References

- Aarnio P et al. (2005). The concentrations and composition of and exposure to fine particles (PM_{2.5}) in the Helsinki subway system. *Atmospheric Environment*, 39(28):5059–5066.
- Abbey DE et al. (1999). Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *American Journal of Respiratory and Critical Care Medicine*, 159(2):373–382.
- Abello N et al. (2009). Protein tyrosine nitration: selectivity, physicochemical and biological consequences, denitration, and proteomics methods for the identification of tyrosine-nitrated proteins. *Journal of Proteome Research*, 8(7):3222–3238.
- Acker K et al. (1998). Atmospheric research program for studying changing emission patterns after German unification. *Atmospheric Environment*, 32(20):3435–3443.
- Adams H. et al. (2001). Fine particle (PM_{2.5}) personal exposure levels in transport microenvironments, London, UK. *Science of the Total Environment*, 279(1–3):29–44.
- Aesif SW et al. (2009). In situ analysis of protein S-glutathionylation in lung tissue using glutaredoxin-1-catalyzed cysteine derivatization. *American Journal of Pathology*, 175(1):36–45.
- Akerstrom M et al. (2013). Associations between urinary excretion of cadmium and proteins in a nonsmoking population: renal toxicity or normal physiology? *Environmental Health Perspectives*, 121(2):187–191.
- Akesson A, Julin B, Wolk A (2008). Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. *Cancer Research*, 68(15):6435–6441.
- Akinaga LMY et al. (2009). Effects of chronic exposure to air pollution from Sao Paulo city on coronary of Swiss mice, from birth to adulthood. *Toxicologic Pathology*, 37(3):306–314.
- Alberg T et al. (2011). Nitrogen dioxide: no influence on allergic sensitization in an intranasal mouse model with ovalbumin and diesel exhaust particles. *Inhalation Toxicology*, 23(5):268–276.
- Alexis NE et al. (2010). Low-level ozone exposure induces airways inflammation and modifies cell surface phenotypes in healthy humans. *Inhalation Toxicology*, 22(7):593–600.

- Allen RW et al. (2011). An air filter intervention study of endothelial function among healthy adults in a woodsmoke-impacted community. *American Journal of Respiratory and Critical Care Medicine*, 183(9):1222–1230.
- Alm S et al. (2001). Personal carbon monoxide exposures of preschool children in Helsinki, Finland – comparison to ambient air concentrations. *Atmospheric Environment*, 35(36):6259–6266.
- Alves CA, Scotto MG, Freitas MC (2010). Air pollution and emergency admissions for cardiorespiratory diseases in Lisbon (Portugal). *Química Nova*, 33(2):337–344.
- Amann M et al. (2008). *Health risks of ozone from long-range transboundary air pollution*. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0005/78647/E91843.pdf, accessed 18 February 2013):93.
- Analitis A, Georgiadis I, Katsouyanni K (2012). Forest fires are associated with elevated mortality in a dense urban setting. *Occupational and Environmental Medicine*, 69(3):158–162.
- Analitis A et al. (2013). Effects of heat waves on mortality: investigation of the effect modification and confounding by air pollutants within the EuroHEAT project. *Epidemiology* (in press).
- Andersen A et al. (1996). Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occupational and Environmental Medicine*, 53(10):708–713.
- Andersen ZJ et al. (2007). Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. *Journal of Exposure Science & Environmental Epidemiology*, 17(7):625–636.
- Andersen ZJ et al. (2008a). Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. *Occupational and Environmental Medicine*, 65(7):458–466.
- Andersen ZJ et al. (2008b). Ambient air pollution triggers wheezing symptoms in infants. *Thorax*, 63(8):710–716.
- Andersen ZJ et al. (2010). Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. *European Heart Journal*, 31(16):2034–2040.
- Andersen ZJ et al. (2012a). Diabetes incidence and long-term exposure to air pollution: a cohort study. *Diabetes Care*, 35(1):92–98.

- Andersen ZJ et al. (2012b). Long-term exposure to air pollution and asthma hospitalisations in older adults: a cohort study. *Thorax*, 67(1):6–11.
- Anderson GB et al. (2012). Is the relation between ozone and mortality confounded by chemical components of particulate matter? Analysis of 7 components in 57 US communities. *American Journal of Epidemiology*, 176(8):726–732.
- Anderson HR, Favarato G, Atkinson RW (2013a). Long-term exposure to outdoor air pollution and the prevalence of asthma: meta-analysis of multi-community prevalence studies. *Air Quality, Atmosphere & Health*: 6(1):57–68.
- Anderson HR, Favarato G, Atkinson RW (2013b). Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Quality, Atmosphere & Health*: 6(1):47–56.
- Anderson HR, Favarato G, Atkinson R (2013c). Erratum to: Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Quality, Atmosphere & Health* 6(2): 541-542.
- Anderson HR et al. (1998). Air pollution, pollens, and daily admissions for asthma in London 1987–92. *Thorax*, 53(10):842–848.
- Anderson HR et al. (2001). Particulate matter and daily mortality and hospital admissions in the West Midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occupational and Environmental Medicine*, 58(8):504–510.
- Anderson HR et al. (2007). *Quantitative systematic review of short term associations between ambient air pollution (particulate matter, ozone, nitrogen dioxide, sulphur dioxide and carbon monoxide), and mortality and morbidity*. London, Department of Health (<https://www.gov.uk/government/publications/quantitative-systematic-review-of-short-term-associations-between-ambient-air-pollution-particulate-matter-ozone-nitrogen-dioxide-sulphur-dioxide-and-carbon-monoxide-and-mortality-and-morbidity>, accessed 15 June 2013).
- Anderson HR et al. (2010). Air pollution and activation of implantable cardioverter defibrillators in London. *Epidemiology*, 21(3):405–413.
- Anenberg SC et al. (2012). Global air quality and health co-benefits of mitigating near-term climate change through methane and black carbon emission controls. *Environmental Health Perspectives*, 120(6):831–839.
- Apte MG, Buchanan ISH, Mendell MJ (2008). Outdoor ozone and building-related symptoms in the BASE study. *Indoor Air*, 18(2):156–170.
- Arbex MA et al. (2010). Impact of outdoor biomass air pollution on hypertension hospital admissions. *Journal of Epidemiology and Community Health*, 64(7):573–579.

- Asmi E et al. (2009). Driver and passenger exposure to aerosol particles in buses and trams in Helsinki, Finland. *Science of the Total Environment*, 407(8):2860–2867.
- Atkinson RW et al. (2001). Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. *American Journal of Respiratory and Critical Care Medicine*, 164(10 Pt 1):1860–1866.
- Atkinson RW et al. (2009). The impact of the congestion charging scheme on ambient air pollution concentrations in London. *Atmospheric Environment*, 43(34):5493–5500.
- Atkinson RW et al. (2010). Urban ambient particle metrics and health: a time-series analysis. *Epidemiology*, 21(4):501–511.
- Atkinson RW et al. (2012a). Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. *Air Quality, Atmosphere & Health*, 5(4):383–391.
- Atkinson RW et al. (2012b). Concentration–response function for ozone and daily mortality: results from five urban and five rural U.K. populations. *Environmental Health Perspectives*, 120(10):1411–1417.
- Atkinson RW et al. (2013). Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology*, 24(1):44–53.
- ATS (2000). American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. *American Journal of Respiratory and Critical Care Medicine*, 161(2 Pt 1):665–673.
- ATSDR (2005). *Toxicological profile for nickel*. Atlanta, GA, Agency for Toxic Substances and Disease Registry (<http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf>, accessed 1 March 2013).
- ATSDR (2007). *Toxicological profile for arsenic*. Atlanta, GA, Agency for Toxic Substances and Disease Registry (<http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf>, accessed 1 March 2013).
- ATSDR (2012). *Toxicological profile for cadmium*. Atlanta, GA, Agency for Toxic Substances and Disease Registry (<http://www.atsdr.cdc.gov/toxprofiles/tp5.pdf>, accessed 1 March 2013).
- Avila-Costa MR et al. (1999). Memory deterioration in an oxidative stress model and its correlation with cytological changes on rat hippocampus CA1. *Neuroscience Letters*, 270(2):107–109.

- Avol EL et al. (2001). Respiratory effects of relocating to areas of differing air pollution levels. *American Journal of Respiratory and Critical Care Medicine*, 164(11):2067–2072.
- Baccini M et al. (2008). Heat effects on mortality in 15 European cities. *Epidemiology*, 19(5):711–719.
- Bahreini R et al. (2012). Gasoline emissions dominate over diesel in formation of secondary organic aerosol mass. *Geophysical Research Letters*, 39(6):L06805:1–6 (<http://www.nserc.und.edu/learning/Bahreini-2012.pdf>, accessed 28 February 2013).
- Bañ N et al. (2011). Maternal exposure to air pollution before and during pregnancy related to changes in newborn's cord blood lymphocyte subpopulations. The EDEN study cohort. *BMC Pregnancy and Childbirth*, 11:87.
- Baja ES et al. (2010). Traffic-related air pollution and QT interval: modification by diabetes, obesity, and oxidative stress gene polymorphisms in the normative aging study. *Environmental Health Perspectives*, 118(6):840–846.
- Bakand S, Winder C, Hayes A (2007). Comparative in vitro cytotoxicity assessment of selected gaseous compounds in human alveolar epithelial cells. *Toxicology in Vitro*, 21(7):1341–1347.
- Bakand S, Hayes A, Dechsakulthorn F (2012). Nanoparticles: a review of particle toxicology following inhalation exposure. *Inhalation Toxicology*, 24(2):125–135.
- Balazy M, Chemtob S (2008). Trans-arachidonic acids: new mediators of nitro-oxidative stress. *Pharmacology & Therapeutics*, 119(3):275–290.
- Ballester F et al. (2002). The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. *Occupational and Environmental Medicine*, 59(5):300–308.
- Ballester F et al. (2006). Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. *Journal of Epidemiology & Community Health*, 60(4):328–336.
- Barbato DL et al. (2010). Traffic air pollution and oxidatively generated DNA damage: can urinary 8-oxo-7,8-dihydro-2-deoxyguanosine be considered a good biomarker? A meta-analysis. *Biomarkers*, 15(6):538–545.
- Barck C et al. (2002). Ambient level of NO₂ augments the inflammatory response to inhaled allergen in asthmatics. *Respiratory Medicine*, 96(11):907–917.
- Barck C et al. (2005). Brief exposures to NO₂ augment the allergic inflammation in asthmatics. *Environmental Research*, 97(1):58–66.

- Barnett AG et al. (2005). Air pollution and child respiratory health – A case-crossover study in Australia and new Zealand. *American Journal of Respiratory and Critical Care Medicine*, 171(11):1272–1278.
- Barraza-Villarreal A et al. (2008). Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. *Environmental Health Perspectives*, 116(6):832–838.
- Barrett EG et al. (2011). Effects of simulated downwind coal combustion emissions on pre-existing allergic airway responses in mice. *Inhalation Toxicology*, 23(13):792–804.
- Barth PJ et al. (1994). Assessment of proliferative activity in type II pneumocytes after inhalation of NO₂ by AgNOR-analysis. *Experimental and Toxicologic Pathology*, 46(4–5):335–342.
- Basile JN, Bloch MJ (2012). Exposure to air pollution increases the incidence of hypertension and diabetes in black women living in Los Angeles. *Journal of Clinical Hypertension*, 14(11):819–820.
- Basu R, Feng WY, Ostro BD (2008). Characterizing temperature and mortality in nine California counties. *Epidemiology*, 19(1):138–145.
- Bauer M et al. (2010). Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study. *Journal of the American College of Cardiology*, 56(22):1803–1808.
- Bauer MA et al. (1986). Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. *American Review of Respiratory Disease*, 134(6):1203–1208.
- Baxter LK et al. (2007). Predictors of concentrations of nitrogen dioxide, fine particulate matter, and particle constituents inside of lower socioeconomic status urban homes. *Journal of Exposure Science & Environmental Epidemiology*, 17(5):433–444.
- Bechtel DG, Waldner CL, Wickstrom M (2009a). Associations between in utero exposure to airborne emissions from oil and gas production and processing facilities and immune system outcomes in neonatal beef calves. *Archives of Environmental & Occupational Health*, 64(1):59–71.
- Bechtel DG, Waldner CL, Wickstrom M (2009b). Associations between immune function in yearling beef cattle and airborne emissions of sulfur dioxide, hydrogen sulfide, and VOCs from oil and natural gas facilities. *Archives of Environmental & Occupational Health*, 64(1):73–86.

- Beckerman BS et al. (2012). The association between chronic exposure to traffic-related air pollution and ischemic heart disease. *Journal of Toxicology and Environmental Health, Part A*, 75(7):402–411.
- Beelen R et al. (2008a). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environmental Health Perspectives*, 116(2):196–202.
- Beelen R et al. (2008b). Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology*, 19(5):702–710.
- Behndig AF et al. (2006). Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans. *European Respiratory Journal*, 27(2):359–365.
- Bekö G et al. (2006). Initial studies of oxidation processes on filter surfaces and their impact on perceived air quality. *Indoor Air*, 16(1):56–64.
- Bell ML, Peng RD, Dominici F (2006). The exposure–response curve for ozone and risk of mortality and the adequacy of current ozone regulations. *Environmental Health Perspectives*, 114(4):532–536.
- Bell ML, Dominici F (2008). Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 US communities. *American Journal of Epidemiology*, 167(8):986–997.
- Bell ML, Levy JK, Lin Z (2008). The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. *Occupational and Environmental Medicine*, 65(2):104–111.
- Bell ML, Morgenstern RD, Harrington W (2011). Quantifying the human health benefits of air pollution policies: Review of recent studies and new directions in accountability research. *Environmental Science & Policy*, 14(4):357–368.
- Bell ML et al. (2009a). Hospital admissions and chemical composition of fine particle air pollution. *American Journal of Respiratory and Critical Care Medicine*, 179(12):1115–1120.
- Bell ML et al. (2009b). Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide: results for 126 United States urban counties, 1999–2005. *Circulation*, 120(11): 949–955.
- Bell ML et al. (2010). Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. *Epidemiology*, 21(6):884–891.

- Bellander T, Wichmann J, Lind T (2012). Individual exposure to NO₂ in relation to spatial and temporal exposure indices in Stockholm, Sweden: the INDEX study. *PLoS ONE*, 7(6):e39536.
- Bellinger DC et al. (2006). Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. *Journal of the American Medical Association*, 295(15):1775–1783.
- Bemis JC, Torous DK, Dertinger SD (2012). *Part 2. Assessment of genotoxicity after exposure to diesel exhaust from US-2007-compliant diesel engines: report on 1- and 3-month exposures in the ACES bioassay*. Boston, Health Effects Institute (Research Report 166; <http://pubs.healtheffects.org/getfile.php?u=709>, accessed 17 March 2013):121–158.
- Benbrahim-Tallaa L et al. (2012). Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncology*, 13(7):663–664.
- Berglund N et al. (2009). Ambient air pollution and daily mortality among survivors of myocardial infarction. *Epidemiology*, 20(1):110–118.
- Berhane K et al. (2011). The effect of ambient air pollution on exhaled nitric oxide in the Children’s Health Study. *European Respiratory Journal*, 37(5):1029–1036.
- Berlin M, Fowler BA, Zalups R (2007). Mercury. In: Nordberg G et al., eds. *Handbook on the toxicology of metals*, 3rd ed. London, Elsevier:675–729.
- Bevelander M et al. (2007). Nitrogen dioxide promotes allergic sensitization to inhaled antigen. *Journal of Immunology*, 179(6):3680–3688.
- Biggeri A, Bellini P, Terracini B (2001). [Meta-analysis of the Italian studies on short-term effects of air pollution]. *Epidemiologia e Prevenzione*, 25(2 Suppl.):1–71 (in Italian).
- Bignami G et al. (1994). Limited effects of ozone exposure during pregnancy on physical and neurobehavioral development of CD-1 mice. *Toxicology and Applied Pharmacology*, 129(2):264–271.
- Billionnet C, Sherrill D, Annesi-Maesano I (2012). Estimating the health effects of exposure to multi-pollutant mixture. *Annals of Epidemiology*, 22(2):126–141.
- Bind MA et al. (2012). Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigene-environment interactions in an elderly cohort. *Epidemiology*, 23(2):332–340.
- Biswas S et al. (2009). Oxidative potential of semi-volatile and non volatile particulate matter (PM) from heavy-duty vehicles retrofitted with emission control technologies. *Environmental Science & Technology*, 43(10):3905–3912.

- Blomberg A et al. (1999). Persistent airway inflammation but accommodated antioxidant and lung function responses after repeated daily exposure to nitrogen dioxide. *American Journal of Respiratory and Critical Care Medicine*, 159(2):536–543.
- Blondeau P et al. (2005). Relationship between outdoor and indoor air quality in eight French schools. *Indoor Air*, 15(1):2–12.
- Boezen HM et al. (1999). Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. *Lancet*, 353(9156):874–878.
- Boldo E et al. (2006). Aphis: Health impact assessment of long-term exposure to PM(2.5) in 23 European cities. *European Journal of Epidemiology*, 21(6):449–458.
- Bølling AK et al. (2012). Wood smoke particles from different combustion phases induce similar pro-inflammatory effects in a co-culture of monocyte and pneumocyte cell lines. *Particle and Fibre Toxicology*, 9:45.
- Bonassi S et al. (2008). Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. *Carcinogenesis*, 29(6):1178–1183.
- Bond TC et al. (2013). Bounding the role of black carbon in the climate system: a scientific assessment. *Journal of Geophysical Research: Atmospheres* (doi: 10.1002/jgrd.50171; <http://onlinelibrary.wiley.com/doi/10.1002/jgrd.50171/pdf>, accessed 28 February 2013).
- Boogaard H et al. (2012a). Contrasts in oxidative potential and other particulate matter characteristics collected near major streets and background locations. *Environmental Health Perspectives*, 120(2):185–191.
- Boogaard H et al. (2012b). Impact of low emission zones and local traffic policies on ambient air pollution concentrations. *Science of the Total Environment*, 435–436:132–140.
- Börjesson M et al. (2012). *The Stockholm congestion charges – five years on. Effects, acceptability and lessons learnt*. Stockholm, Centre for Transport Studies (http://ideas.repec.org/p/hhs/ctswps/2012_003.html, accessed 8 February 2013).
- Bosson J et al. (2008). Diesel exhaust exposure enhances the ozone-induced airway inflammation in healthy humans. *European Respiratory Journal*, 31(6):1234–1240.
- Boström CE et al. (2002). Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environmental Health Perspectives*, 110(Suppl. 3):451–488.

- Brandsma CA et al. (2008). Nitrogen dioxide exposure attenuates cigarette smoke-induced cytokine production in mice. *Inhalation Toxicology*, 20(2):183–189.
- Brandt SJ et al. (2012). Costs of childhood asthma due to traffic-related pollution in two California communities. *European Respiratory Journal*, 40(2):363–370.
- Braubach M et al. (2013). Mortality associated with exposure to carbon monoxide in WHO European Member States. *Indoor Air*, 23(2):115–125.
- Brauer M, Brook JR (1995). Personal and fixed-site ozone measurements with a passive sampler. *Journal of the Air & Waste Management Association*, 45(7):529–537.
- Brauer M et al. (2007). Air pollution and development of asthma, allergy and infections in a birth cohort. *European Respiratory Journal*, 29(5):879–888.
- Brauer M et al. (2008). A cohort study of traffic-related air pollution impacts on birth outcomes. *Environmental Health Perspectives*, 116(5):680–686.
- Bräuner EV et al. (2008). Indoor particles affect vascular function in the aged: an air filtration-based intervention study. *American Journal of Respiratory and Critical Care Medicine*, 177(4):419–425.
- Breitner S et al. (2009). Short-term mortality rates during a decade of improved air quality in Erfurt, Germany. *Environmental Health Perspectives*, 117(3):448–454.
- Briet M et al. (2007). Endothelial function and chronic exposure to air pollution in normal male subjects. *Hypertension*, 50(5):970–976.
- Bronzetti G et al. (1997). Mutagenicity and chemical analysis of airborne particulate matter collected in Pisa. *Journal of Environmental Pathology, Toxicology and Oncology*, 16(2–3):147–156.
- Brook JR et al. (2007). Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. *Journal of Exposure Science & Environmental Epidemiology*, 17(Suppl. 2):S36–S44.
- Brook RD et al. (2008). The relationship between diabetes mellitus and traffic-related air pollution. *Journal of Occupational and Environmental Medicine*, 50(1):32–38.
- Brook RD et al. (2010). Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*, 121(21):2331–2378.
- Brook RD et al. (2013). Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. *Science of the Total Environment*, 448:66–71.

- Brown JS, Bateson TF, McDonnell WF (2008). Effects of exposure to 0.06 ppm ozone on FEV1 in humans: a secondary analysis of existing data. *Environmental Health Perspectives*, 116(8):1023–1026.
- Brown SM et al. (1975). Effect on mortality of the 1974 fuel crisis. *Nature*, 257(5524):306–307.
- Bruinen de Bruin Y et al. (2004). Personal carbon monoxide exposure levels: contribution of local sources to exposures and microenvironment concentrations in Milan. *Journal of Exposure Analysis and Environmental Epidemiology*, 14(4):312–322.
- Brunekreef B (2007). Health effects of air pollution observed in cohort studies in Europe. *Journal of Exposure Science & Environmental Epidemiology*, 17(Suppl. 2):S61–S65.
- Brunekreef B, Forsberg B (2005). Epidemiological evidence of effects of coarse airborne particles on health. *European Respiratory Journal*, 26(2):309–318.
- Brunekreef B et al. (1994). Respiratory effects of low-level photochemical air pollution in amateur cyclists. *American Journal of Respiratory and Critical Care Medicine*, 150(4):962–966.
- Brunekreef B et al. (1997). Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology*, 8(3):298–303.
- Brunekreef B et al. (2005). *Personal, indoor, and outdoor exposures to PM_{2.5} and its components for groups of cardiovascular patients in Amsterdam and Helsinki*. Boston, Health Effects Institute (Research Report 127; <http://pubs.healtheffects.org/getfile.php?u=126>, accessed 16 March 2013):1–70; discussion: 71–79.
- Brüske I et al. (2011). Ambient air pollution and lipoprotein-associated phospholipase A₂ in survivors of myocardial infarction. *Environmental Health Perspectives*, 119(7):921–926.
- Bünger J et al. (2000). Cytotoxic and mutagenic effects, particle size and concentration analysis of diesel engine emissions using biodiesel and petrol diesel as fuel. *Archives of Toxicology*, 74(8):490–498.
- Bünger J et al. (2007). Strong mutagenic effects of diesel engine emissions using vegetable oil as fuel. *Archives of Toxicology*, 81(8):599–603.
- Burgan O et al. (2010). Cardiovascular effects of sub-daily levels of ambient fine particles: a systematic review. *Environmental Health* (doi: 10.1186/1476-069X-9-26; <http://www.ehjournal.net/content/9/1/26>, accessed 28 February 2013).

- Burnett RT, Cakmak S, Brook JR (1998). The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. *Canadian Journal of Public Health*, 89(3):152–156.
- Burnett RT et al. (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Archives of Environmental Health*, 59(5):228–236.
- Burnett RT et al. (under review). An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure.
- Burr ML et al. (2004). Effects on respiratory health of a reduction in air pollution from vehicle exhaust emissions. *Occupational and Environmental Medicine*, 61(3):212–218.
- Burra TA et al. (2009). Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. *Environmental Research*, 109(5):567–574.
- Burstyn I et al. (2005). Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. *Epidemiology*, 16(6):744–750.
- Bylin G et al. (1985). Effects of short-term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function. *European Journal of Respiratory Diseases*, 66(3):205–217.
- Bylin G et al. (1988). Ambient nitrogen dioxide concentrations increase bronchial responsiveness in subjects with mild asthma. *European Respiratory Journal*, 1(7):606–612.
- Caamano-Isorna F et al. (2011). Respiratory and mental health effects of wildfires: an ecological study in Galician municipalities (north-west Spain). *Environmental Health* (doi: 10.1186/1476-069X-10-48; <http://www.ehjournal.net/content/10/1/48>, accessed 28 February 2013).
- CAFE (2005). *CAFE CBA: Baseline Analysis 2000 to 2020 – Service Contract for carrying out cost-benefit analysis of air quality related issues, in particular in the Clean Air for Europe (CAFE) Programme*. Didcot, AEA Technology Environment (AEAT/ED51014/Baseline Scenarios: Issue 5; http://ec.europa.eu/environment/archives/cape/activities/pdf/cba_baseline_results2000_2020.pdf, accessed 14 March 2013).
- Cai C et al. (2008). Prior SO₂ exposure promotes airway inflammation and subepithelial fibrosis following repeated ovalbumin challenge. *Clinical and Experimental Allergy*, 38(10):1680–1687.

- Cakmak S, Dales RE, Judek S (2006a). Do gender, education, and income modify the effect of air pollution gases on cardiac disease? *Journal of Occupational and Environmental Medicine*, 48(1):89–94.
- Cakmak S, Dales RE, Judek S (2006b). Respiratory health effects of air pollution gases: modification by education and income. *Archives of Environmental & Occupational Health*, 61(1):5–10.
- Cakmak S, Dales RE, Vidal CB (2007). Air pollution and mortality in Chile: susceptibility among the elderly. *Environmental Health Perspectives*, 115(4):524–527.
- Cakmak S et al. (2009). Components of particulate air pollution and emergency department visits in Chile. *Archives of Environmental & Occupational Health*, 64(3):148–155.
- Calderón-Garcidueñas L et al. (2002). Air pollution and brain damage. *Toxicologic Pathology*, 30(3):373–389.
- Calogero AE et al. (2011). Environmental car exhaust pollution damages human sperm chromatin and DNA. *Journal of Endocrinological Investigation*, 34(6):e139–e143.
- Canova C et al. (2010). Carbon monoxide pollution is associated with decreased lung function in asthmatic adults. *European Respiratory Journal*, 35(2):266–272.
- Cao J et al. (2011). Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *Journal of Hazardous Materials*, 186(2–3):1594–1600.
- CARB (2007). *Review of the California ambient air quality standard for nitrogen dioxide*. Sacramento, California Environmental Protection Agency Air Resources Board. (<http://www.arb.ca.gov/research/aaqs/no2-rs/no2-doc.htm#TechSuppDoc>, accessed 1 March 2013).
- Carbajal-Arroyo L et al. (2011). Effect of PM₁₀ and O₃ on infant mortality among residents in the Mexico City Metropolitan Area: a case-crossover analysis, 1997–2005. *Journal of Epidemiology and Community Health*, 65(8):715–721.
- Carey SA et al. (2011). Persistent rhinitis and epithelial remodeling induced by cyclic ozone exposure in the nasal airways of infant monkeys. *American Journal of Physiology – Lung Cellular and Molecular Physiology*, 300(2):L242–L254.
- Carlsten C et al. (2011a). Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occupational and Environmental Medicine*, 68(4):291–295.

- Carlsten C et al. (2011b). GSTP1 polymorphism modifies risk for incident asthma associated with nitrogen dioxide in a high-risk birth cohort. *Occupational and Environmental Medicine*, 68(4):308.
- Casati R et al. (2007). Measurement of nucleation and soot mode particle emission from a diesel passenger car in real world and laboratory in situ dilution. *Atmospheric Environment*, 41(10):2125–2135.
- Castellanos P, Boersma KF (2012). Reductions in nitrogen oxides over Europe driven by environmental policy and economic recession. *Scientific Reports*, 2:265.
- Castro HA et al. (2009). Effect of air pollution on lung function in schoolchildren in Rio de Janeiro, Brazil. *Revista de Saúde Pública*, 43(1):26–34.
- Castro-Giner F et al. (2009). Traffic-related air pollution, oxidative stress genes, and asthma (ECHRS). *Environmental Health Perspectives*, 117(12):1919–1924.
- Cavalli F et al. (2010). Toward a standardised thermal-optical protocol for measuring atmospheric organic and elemental carbon: the EUSAAR protocol. *Atmospheric Measurement Techniques*, 3(1):79–89.
- Cesaroni G et al. (2012). Health benefits of traffic-related air pollution reduction in different socioeconomic groups: the effect of low-emission zoning in Rome. *Occupational and Environmental Medicine*, 69(2):133–139.
- Cesaroni G et al. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environmental Health Perspectives*, 121(3):324–331.
- Chan AT, Chung MW (2003). Indoor–outdoor air quality relationships in vehicle: effect of driving environment and ventilation modes. *Atmospheric Environment*, 37(27):3795–3808.
- Chan CC, Wu TH (2005). Effects of ambient ozone exposure on mail carriers' peak expiratory flow rates. *Environmental Health Perspectives*, 113(6):735–738.
- Chan CC, Ng HC (2011). A case-crossover analysis of Asian dust storms and mortality in the downwind areas using 14-year data in Taipei. *Science of the Total Environment*, 410-411:47–52.
- Chan CC et al. (2008). Increasing cardiopulmonary emergency visits by long-range transported Asian dust storms in Taiwan. *Environmental Research*, 106(3):393–400.
- Chan TC et al. (2009). Spatiotemporal analysis of air pollution and asthma patient visits in Taipei, Taiwan. *International Journal of Health Geographics*, 8:26.

- Chang T, Hsia Y, Chen WL (2002). Effect of air pollution on daily clinic treatments for respiratory cardiovascular disease in central Taiwan, 1997–1999. *Taiwan Occupational Medicine Journal*, (9):111–120 (in Chinese).
- Chang YK et al. (2012). The short-term effects of air pollution on adolescent lung function in Taiwan. *Chemosphere*, 87(1):26–30.
- Channell MM et al. (2012). Circulating factors induce coronary endothelial cell activation following exposure to inhaled diesel exhaust and nitrogen dioxide in humans: evidence from a novel translational in vitro model. *Toxicological Sciences*, 127(1):179–186.
- Charrier JG, Anastasio C (2011). Impacts of antioxidants on hydroxyl radical production from individual and mixed transition metals in a surrogate lung fluid. *Atmospheric Environment*, 45(40):7555–7562.
- Chaumont A et al. (2012). Associations between proteins and heavy metals in urine at low environmental exposures: evidence of reverse causality. *Toxicology Letters*, 210(3):345–352.
- Chay KY, Greenstone M (2003). The impact of air pollution on infant mortality: evidence from geographic variation in pollution shocks induced by a recession. *Quarterly Journal of Economics*, 118(3):1121–1167.
- Chen C, Zhao B (2011). Review of relationship between indoor and outdoor particles: I/O ratio, infiltration factor and penetration factor. *Atmospheric Environment*, 45(2):275–288.
- Chen C, Zhao B, Weschler CJ (2012). Assessing the influence of indoor exposure to “outdoor ozone” on the relationship between ozone and short-term mortality in U.S. communities. *Environmental Health Perspectives*, 120(2):235–240.
- Chen G et al. (2008). Short-term effects of ambient gaseous pollutants and particulate matter on daily mortality in Shanghai, China. *Journal of Occupational Health*, 50(1):41–47.
- Chen JC, Schwartz J (2009). Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology*, 30(2):231–239.
- Chen LH et al. (2005). The association between fatal coronary heart disease and ambient particulate air pollution: are females at greater risk? *Environmental Health Perspectives*, 113(12):1723–1729.
- Chen R et al. (2010a). Ambient air pollution and daily mortality in Anshan, China: a time-stratified case-crossover analysis. *Science of the Total Environment*, 408(24):6086–6091.

- Chen R et al. (2010b). Ambient air pollution and hospital admission in Shanghai, China. *Journal of Hazardous Materials*, 181(1–3):234–240.
- Chen R et al. (2011). Coarse particles and mortality in three Chinese cities: the China Air Pollution and Health Effects Study (CAPES). *Science of the Total Environment*, 409(23):4934–4938.
- Chen R et al. (2012a). Association of particulate air pollution with daily mortality: the China Air Pollution and Health Effects Study. *American Journal of Epidemiology*, 175(11):1173–1181.
- Chen R et al. (2012b). Associations between short-term exposure to nitrogen dioxide and mortality in 17 Chinese cities: the China Air Pollution and Health Effects Study (CAPES). *Environment International*, 45:32–38.
- Chen R et al. (2012c). Short-term exposure to sulfur dioxide and daily mortality in 17 Chinese cities: the China air pollution and health effects study (CAPES). *Environmental Research*, 118:101–106.
- Chen R et al. (2013). Communicating air pollution-related health risks to the public: an application of the Air Quality Health Index in Shanghai, China. *Environment International*, 51:168–173.
- Chen SS et al. (2011). Sulfur dioxide acts as a novel endogenous gaseous signaling molecule in the cardiovascular system. *Chinese Medical Journal*, 124(12):1901–1905.
- Chen X, Hopke PK (2010). A chamber study of secondary organic aerosol formation by limonene ozonolysis. *Indoor Air*, 20(4):320–328.
- Chen X, Hopke PK, Carter WPL (2011). Secondary organic aerosol from ozonolysis of biogenic volatile organic compounds: chamber studies of particle and reactive oxygen species formation. *Environmental Science & Technology*, 45(1):276–282.
- Chiusolo M et al. (2011). Short term effects of nitrogen dioxide on mortality and susceptibility factors in ten Italian Cities: the EpiAir Study. *Environmental Health Perspectives*, 119(9):1233–1238.
- Choi H, Perera FP (2012). Sources of greater fetal vulnerability to airborne polycyclic aromatic hydrocarbons among African Americans. *Journal of Epidemiology and Community Health*, 66(2):121–126.
- Choi H et al. (2012). Fetal window of vulnerability to airborne polycyclic aromatic hydrocarbons on proportional intrauterine growth restriction. *PloS ONE*, 7(4):e35464.

- Chuang GC et al. (2009). Pulmonary ozone exposure induces vascular dysfunction, mitochondrial damage, and atherogenesis. *American Journal of Physiology – Lung Cellular and Molecular Physiology*, 297(2):L209–L216.
- Chuang KJ et al. (2007). The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *American Journal of Respiratory and Critical Care Medicine*, 176(4):370–376.
- Chuang KJ et al. (2011). Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. *Occupational and Environmental Medicine*, 68(1):64–68.
- Ciarrocca M et al. (2011). Follicle-stimulating hormone levels in female workers exposed to urban pollutants. *International Journal of Environmental Health Research*, 21(6):391–401.
- Clancy L et al. (2002). Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet*, 360(9341):1210–1214.
- Clark NA et al. (2010). Effect of early life exposure to air pollution on development of childhood asthma. *Environmental Health Perspectives*, 118(2):284–290.
- Clarkson TW, Magos L (2006). The toxicology of mercury and its chemical compounds. *Critical Reviews in Toxicology*, 36(8):609–662.
- Clausen PA et al. (2001). Chemical and biological evaluation of a reaction mixture of R-(+)-limonene/ozone: formation of strong airway irritants. *Environment International*, 26(7-8):511–522.
- Cocheo V et al. (2000). Urban benzene and population exposure. *Nature*, 404(6774):141–142.
- Cohen AJ et al. (2005). The global burden of disease due to outdoor air pollution. *Journal of Toxicology and Environmental Health, Part A*, 68(13–14):1301–1307.
- Colais P et al. (2009). [Air pollution and urgent hospital admissions in nine Italian cities: results of the EpiAir Project]. *Epidemiologia e Prevenzione*, 33(6 Suppl. 1):77–94 (in Italian).
- Colais P et al. (2012). Particulate air pollution and hospital admissions for cardiac diseases in potentially sensitive subgroups. *Epidemiology*, 23(3):473–481.
- COMEAP (2006). *Cardiovascular disease and air pollution*. London, Department of Health Committee on the Medical Effects of Air Pollutants (<http://www.comeap.org.uk/documents>, accessed 15 June 2013).

- COMEAP (2009a). *Long-term exposure to air pollution: effect on mortality*. London, Department of Health Committee on the Medical Effects of Air Pollutants (<http://www.comeap.org.uk/documents>, accessed 15 June 2013).
- COMEAP (2009b). *Statement on the quantification of the effects of long-term exposure to nitrogen dioxide*. London, Department of Health Committee on the Medical Effects of Air Pollutants (<http://www.comeap.org.uk/documents>, accessed 15 June 2013).
- COMEAP (2010). *The mortality effects of long-term exposure to particulate air pollution in the United Kingdom*. London, Department of Health Committee on the Medical Effects of Air Pollutants (<http://www.comeap.org.uk/documents>, accessed 15 June 2013).
- Coneus K, Spiess CK (2012). Pollution exposure and child health: evidence for infants and toddlers in Germany. *Journal of Health Economics*, 31(1):180–196.
- Conklin DJ, Kong M (2012). *Part 4. Effects of subchronic diesel engine emissions exposure on plasma markers in rodents: report on 1- and 3-month exposures in the ACES bioassay*. Boston, Health Effects Institute (Research Report 166; <http://pubs.healtheffects.org/getfile.php?u=709>, accessed 17 March 2013):189–223.
- Conolly C (2009). *Annual Report for 2007 on the UK PAH Monitoring and Analysis Network*. London, Department for Environment, Food and Rural Affairs (http://uk-air.defra.gov.uk/reports/cat05/0909031320_PAH_Network_Annual_Report_2007_v8_final.pdf, accessed 1 March 2013).
- CONTAM (2009). Scientific opinion on cadmium in food. *EFSA Journal*, (980):1–149.
- CONTAM (2010). Scientific opinion on lead in food. *EFSA Journal*, 8(4):1–147.
- Coogan PF et al. (2012). Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. *Circulation*, 125(6):767–772.
- Cooke RM et al. (2007). A probabilistic characterization of the relationship between fine particulate matter and mortality: elicitation of European experts. *Environmental Science & Technology*, 41(18):6598–6605.
- Correia AW et al. (2013). Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. *Epidemiology*, 24(1):23–31.
- Crouse DL et al. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environmental Health Perspectives*, 120(5):708–714.

- Cyrus J et al. (2012). Variation of NO₂ and NO_x concentrations between and within 36 European study areas: results from the ESCAPE study. *Atmospheric Environment*, 62:374–390.
- Dadvand P et al. (2011). Saharan dust episodes and pregnancy. *Journal of Environmental Monitoring*, 13(11):3222–3228.
- Dales R et al. (2004). Air pollution and sudden infant death syndrome. *Pediatrics*, 113(6):e628–e631.
- Dales R et al. (2009). Acute effects of outdoor air pollution on forced expiratory volume in 1 s: a panel study of schoolchildren with asthma. *European Respiratory Journal*, 34(2):316–323.
- D'Amato G et al. (2005). Environmental risk factors and allergic bronchial asthma. *Clinical and Experimental Allergy*, 35(9):1113–1124.
- Damera G et al. (2010). Inhibition of myristoylated alanine-rich C kinase substrate (MARCKS) protein inhibits ozone-induced airway neutrophilia and inflammation. *Experimental Lung Research*, 36(2):75–84.
- Davis ME (2012). Recessions and health: the impact of economic trends on air pollution in California. *American Journal of Public Health*, 102(10):1951–1956.
- DEFRA (1999). Polycyclic Aromatic Hydrocarbons [web site]. Norwich, Department for Environment, Food & Rural Affairs
(<http://webarchive.nationalarchives.gov.uk/20060715141954/http://www.defra.gov.uk/environment/airquality/aqs/poly/index.htm>, accessed 29 March 2013).
- DEFRA (2007). *The Air Quality Strategy for England, Scotland, Wales and Northern Ireland*. Vol. 1. Norwich, Department for Environment, Food and Rural Affairs in partnership with the Scottish Executive, Welsh Assembly Government and Department of the Environment Northern Ireland
(<http://www.defra.gov.uk/publications/files/pb12654-air-quality-strategy-vol1-070712.pdf>, accessed 5 April 2013).
- De Hartog JJ et al. (2009). Associations between PM_{2.5} and heart rate variability are modified by particle composition and beta-blocker use in patients with coronary heart disease. *Environmental Health Perspectives*, 117(1):105–111.
- Delfino RJ et al. (2006). Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. *Environmental Health Perspectives*, 114(11):1736–1743.
- Delfino RJ et al. (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in

- subjects with coronary artery disease. *Environmental Health Perspectives*, 116(7):898–906.
- Delfino RJ et al. (2009a). The relationship of respiratory and cardiovascular hospital admissions to the southern California wildfires of 2003. *Occupational and Environmental Medicine*, 66(3):189–197.
- Delfino RJ et al. (2009b). Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environmental Health Perspectives*, 117(8):1232–1238.
- Delfino RJ et al. (2010a). Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. *Epidemiology*, 21(3):396–404.
- Delfino RJ et al. (2010b). Associations of primary and secondary organic aerosols with airway and systemic inflammation in an elderly panel cohort. *Epidemiology*, 21(6):892–902.
- Delfino RJ et al. (2011). Electrocardiographic ST-segment depression and exposure to traffic-related aerosols in elderly subjects with coronary artery disease. *Environmental Health Perspectives*, 119(2):196–202.
- Delgado-Saborit JM, Stark C, Harrison RM (2011). Carcinogenic potential, levels and sources of polycyclic aromatic hydrocarbon mixtures in indoor and outdoor environments and their implications for air quality standards. *Environment International*, 37(2):383–392.
- Delgado-Saborit JM et al. (2009). Measurement of personal exposure to volatile organic compounds and particle associated PAH in three UK regions. *Environmental Science & Technology*, 43(12):4582–4588.
- Dellinger B et al. (2008). Report: combustion byproducts and their health effects: summary of the 10th International Congress. *Environmental Engineering Science*, 25(8):1107–1114.
- De Rosa M et al. (2003). Traffic pollutants affect fertility in men. *Human Reproduction*, 18(5):1055–1061.
- DeRouen TA et al. (2006). Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. *Journal of the American Medical Association*, 295(15):1784–1792.
- Derwent RG et al. (2010). Ozone in Central England: the impact of 20 years of precursor emission controls in Europe. *Environmental Science & Policy*, 13(3):195–204.
- Devlin RB et al. (1999). Inflammatory response in humans exposed to 2.0 ppm nitrogen dioxide. *Inhalation Toxicology*, 11(2):89–109.

- Devlin RB et al. (2003). Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *European Respiratory Journal. Supplement*, 40:76s–80s.
- Díaz J, Linares C, Tobías A (2006). Impact of extreme temperatures on daily mortality in Madrid (Spain) among the 45–64 age-group. *International Journal of Biometeorology*, 50(6):342–348.
- Diaz-Sanchez D et al. (1999). Effect of topical fluticasone propionate on the mucosal allergic response induced by ragweed allergen and diesel exhaust particle challenge. *Clinical Immunology*, 90(3):313–322.
- Dimitrios K et al. (2009). Exposure to multiple air contaminants in public buildings, schools and kindergartens – the European Indoor Air Monitoring and Exposure Assessment (AIRMEX) Study. *Fresenius Environmental Bulletin*, 18(5a): 670–681.
- d’Ischia M et al. (2011). Secondary targets of nitrite-derived reactive nitrogen species: nitrosation/nitration pathways, antioxidant defense mechanisms and toxicological implications. *Chemical Research in Toxicology*, 24(12):2071–2092.
- Dockery DW et al. (1993). An association between air pollution and mortality in six U.S. cities. *New England Journal of Medicine*, 329(24):1753–1759.
- Dockery DW et al. (2013). *Effect of air pollution control on mortality and hospital admissions in Ireland*. Boston, Health Effects Institute (Research Report 176).
- Dominici F et al. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *Journal of the American Medical Association*, 295(10):1127–1134.
- Dominici F et al. (2007a). Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? *American Journal of Epidemiology*, 166(8):880–888.
- Dominici F et al. (2007b). Does the effect of PM10 on mortality depend on PM nickel and vanadium content? A reanalysis of the NMMAPS data. *Environmental Health Perspectives*, 115(12):1701–1703.
- Dong GH et al. (2011). Gender differences and effect of air pollution on asthma in children with and without allergic predisposition: Northeast Chinese Children Health Study. *PLoS ONE*, 6(7):e22470.
- Dorado-Martínez C et al. (2001). Effects of different ozone doses on memory, motor activity and lipid peroxidation levels, in rats. *International Journal of Neuroscience*, 108(3–4):149–161.

- Downs SH et al. (2007). Reduced exposure to PM₁₀ and attenuated age-related decline in lung function. *New England Journal of Medicine*, 357(23):2338–2347.
- Duffin R, Mills NL, Donaldson K (2007). Nanoparticles – a thoracic toxicology perspective. *Yonsei Medical Journal*, 48(4):561–572.
- Ebelt S et al. (2001). Air quality in postunification Erfurt, East Germany: associating changes in pollutant concentrations with changes in emissions. *Environmental Health Perspectives*, 109(4):325–333.
- EC (2001). *Ambient air pollution by polycyclic aromatic hydrocarbons (PAH)*. Position paper. Luxembourg, Office for Official Publications of the European Communities (http://ec.europa.eu/environment/air/pdf/pp_pah.pdf, accessed 29 March 2013).
- EC (2012). Air quality standards [web site]. Brussels, European Commission (<http://ec.europa.eu/environment/air/quality/standards.htm>, accessed 19 February 2013).
- Edwards J, Walters S, Griffiths RK (1994). Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Archives of Environmental Health*, 49(4):223–227.
- Edwards RD, Jantunen MJ (2001). Benzene exposure in Helsinki, Finland. *Atmospheric Environment*, 35(8):1411–1420.
- Edwards SC et al. (2010). Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children’s intelligence at 5 years of age in a prospective cohort study in Poland. *Environmental Health Perspectives*, 118(9):1326–1331.
- EEA (2011). *Impact of selected policy measures on Europe’s air quality*. Copenhagen, European Environment Agency (http://www.eea.europa.eu/publications/impact-of-selected-policy-measures/at_download/file, accessed 30 March 2013).
- EEA (2012). *Air quality in Europe – 2012*. Copenhagen, European Environment Agency (<http://www.eea.europa.eu/publications/air-quality-in-europe-2012>, accessed 27 March 2013).
- Eeftens M et al. (2012a). Development of land use regression models for PM_{2.5}, PM_{2.5} absorbance, PM₁₀ and PM_{coarse} in 20 European study areas; results of the ESCAPE project. *Environmental Science & Technology*, 46(20):11195–11205.
- Eeftens M et al. (2012b). Spatial variation of PM_{2.5}, PM₁₀, PM_{2.5} absorbance and PM_{coarse} concentrations between and within 20 European study areas and the relationship with NO₂ – results of the ESCAPE project. *Atmospheric Environment*, 62:303–317.

- Eenhuizen E et al. (2012). Traffic related air pollution is related to interrupter resistance in four-year old children. *European Respiratory Journal* (doi: 10.1183/09031936.00020812; <http://erj.ersjournals.com/content/early/2012/10/25/09031936.00020812.abstract>, accessed 9 May 2013).
- Eggleston PA (2009). Complex interactions of pollutant and allergen exposures and their impact on people with asthma. *Pediatrics*, 123(Suppl.):S160–S167.
- Ehrlich R, Henry MC (1968). Chronic toxicity of nitrogen dioxide. I. Effect on resistance to bacterial pneumonia. *Archives of Environmental Health*, 17(6):860–865.
- Eilstein D et al. (2004). Programme de surveillance air et Santé 9 villes. *Presse Médicale*, 33(19 Pt 1):1323–1327.
- Eiswerth ME, Douglass Shaw W, Yen ST (2005). Impacts of ozone on the activities of asthmatics: revisiting the data. *Journal of Environmental Management*, 77(1):56–63.
- Elder A et al. (2004). On-road exposure to highway aerosols. 2. Exposures of aged, compromised rats. *Inhalation Toxicology*, 16(Suppl. 1):41–53.
- Elder A et al. (2007). Effects of on-road highway aerosol exposures on autonomic responses in aged, spontaneously hypertensive rats. *Inhalation Toxicology*, 19(1):1–12.
- Eliasson J (2008). Lessons from the Stockholm congestion charging trial. *Transport Policy*, 15(6):395–404.
- Eliasson J et al. (2009). The Stockholm congestion–charging trial 2006: overview of effects. *Transportation Research Part A: Policy and Practice*, 43(3):240–250.
- Enami S, Hoffmann MR, Colussi AJ (2009). Absorption of inhaled NO(2). *Journal of Physical Chemistry B*, 113(23):7977–7981.
- English P et al. (1999). Examining associations between childhood asthma and traffic flow using a geographic information system. *Environmental Health Perspectives*, 107(9):761–767.
- Engström A et al. (2011). Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. *Journal of Bone and Mineral Research*, 26(3):486–495.
- Engström A et al. (2012). Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. *Bone*, 50(6):1372–1378.

- EPA (2006). Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 Final) [web site]. Washington, DC, United States Environmental Protection Agency (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923>, accessed 5 April 2013).
- EPA (2008a). *Integrated science assessment (ISA) for sulfur oxides – health criteria (final report)*. Washington, DC, United States Environmental Protection Agency (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843>, accessed 29 March 2013).
- EPA (2008b). *Integrated science assessment for oxides of nitrogen – health criteria (final report)*. Washington, DC, United States Environmental Protection Agency (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645#Download>, accessed 20 March 2013).
- EPA (2009). *Integrated science assessment for particulate matter (final report)*. Washington, DC, United States Environmental Protection Agency (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546#Download>, accessed 5 April 2013).
- EPA (2010a). *Quantitative health risk assessment for particulate matter: second external review draft*. Research Triangle Park, NC, United States Environmental Protection Agency (<http://www.epa.gov/ttnnaqs/standards/pm/data/20100209RA2ndExternalReviewDraft.pdf>, accessed 5 April 2013).
- EPA (2010b). *IRIS toxicological review of inorganic arsenic (cancer) (2010 external review draft)*. Washington, DC, United States Environmental Protection Agency (http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=219111, accessed 8 February 2013).
- EPA (2012). Integrated Science Assessment of Ozone and Related Photochemical Oxidants (Second External Review Draft) [web site]. Washington, DC, United States Environmental Protection Agency (<http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=226363>, accessed 21 February 2013).
- EPA (2013). EPA integrated science assessments [web site]. EPA's integrated science assessment on air quality. Washington, DC, United States Environmental Protection Agency (<http://www.epa.gov/ncea/isa/>, accessed 18 February 2013).
- EPA Region 8 (2013). Risk Characterization [web site]. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/region8/r8risk/hh_risk.html, accessed 25 February 2013).
- EPAQS (2009). *Metals and metalloids*. London, Department for Environment, Food and Rural Affairs

- (<http://archive.defra.gov.uk/environment/quality/air/airquality/panels/aqs/documents/metals-and-metalloids.pdf>, accessed 27 March 2013).
- Erbas B, Hyndman RJ (2005). Sensitivity of the estimated air pollution-respiratory admissions relationship to statistical model choice. *International Journal of Environmental Health Research*, 15(6):437–448.
- Escamilla-Nuñez MC et al. (2008). Traffic-related air pollution and respiratory symptoms among asthmatic children, resident in Mexico City: the EVA cohort study. *Respiratory Research*, 9:74.
- EU (2005). Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. *Official Journal of the European Union*, 23(3):1–14.
- EU (2008). Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. *Official Journal of the European Union*, 152(1):1–44.
- Fakhri AA et al. (2009). Autonomic effects of controlled fine particulate exposure in young healthy adults: effect modification by ozone. *Environmental Health Perspectives*, 117(8):1287–1292.
- Fann N et al. (2012). Estimating the national public health burden associated with exposure to ambient PM_{2.5} and ozone. *Risk Analysis*, 32(1):81–95.
- Fanucchi MV et al. (2006). Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *American Journal of Physiology – Lung Cellular and Molecular Physiology*, 291(4):L644–650.
- Faustini A et al. (2012). Short-term effects of air pollution in a cohort of patients with chronic obstructive pulmonary disease. *Epidemiology*, 23(6):861–879.
- Faustini A et al. (2013). Air pollution and multiple acute respiratory outcomes. *European Respiratory Journal* (doi: 10.1183/09031936.00128712; <http://erj.ersjournals.com/content/early/2013/01/10/09031936.00128712.abstract>, accessed 9 May 2013).
- Filleul L et al. (2005). Twenty five year mortality and air pollution: results from the French PAARC survey. *Occupational and Environmental Medicine*, 62(7):453–460.
- Filleul L et al. (2006a). Influence of set-up conditions of exposure indicators on the estimate of short-term associations between urban pollution and mortality. *Science of the Total Environment*, 355(1–3):90–97.

- Filleul L et al. (2006b). The relation between temperature, ozone, and mortality in nine French cities during the heat wave of 2003. *Environmental Health Perspectives*, 114(9):1344–1347.
- Fischer PH et al. (2011). Trends in relative risk estimates for the association between air pollution and mortality in The Netherlands, 1992–2006. *Environmental Research*, 111(1):94–100.
- Floyd HS et al. (2009). Fine ambient air particulate matter exposure induces molecular alterations associated with vascular disease progression within plaques of atherosclerotic susceptible mice. *Inhalation Toxicology*, 21(5):394–403.
- Fondelli MC et al. (2008). Fine particle concentrations in buses and taxis in Florence, Italy. *Atmospheric Environment*, 42(35):8185–8193.
- Forbes LJJ et al. (2009). Chronic exposure to outdoor air pollution and lung function in adults. *Thorax*, 64(8):657–663.
- Forester CD, Wells JR (2009). Yields of carbonyl products from gas-phase reactions of fragrance compounds with OH radical and ozone. *Environmental Science & Technology*, 43(10):3561–3568.
- Foster A, Kumar N (2011). Health effects of air quality regulations in Delhi, India. *Atmospheric Environment*, 45(9):1675–1683.
- Frampton MW, Greaves IA (2009). NO_x–NO_x: who’s there? *American Journal of Respiratory and Critical Care Medicine*, 179(12):1077–1078.
- Frampton MW et al. (1989). Nitrogen dioxide exposure in vivo and human alveolar macrophage inactivation of influenza virus in vitro. *Environmental Research*, 48(2):179–192.
- Frampton MW (2001). Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. *Environmental Health Perspectives*, 109(Suppl. 4):529–532.
- Frampton MW et al. (2002). Nitrogen dioxide exposure: effects on airway and blood cells. *American Journal of Physiology – Lung, Cellular and Molecular Physiology*, 282(1):L155–165.
- Frampton MW et al. (2004). *Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma*. Boston, Health Effects Institute (Research Report 126; <http://pubs.healtheffects.org/getfile.php?u=129>, accessed 17 March 2013).
- Franck U et al. (2011). The effect of particle size on cardiovascular disorders – the smaller the worse. *Science of the Total Environment*, 409(20):4217–4221.

- Franklin M, Zeka A, Schwartz J (2007). Association between PM_{2.5} and all-cause and specific-cause mortality in 27 US communities. *Journal of Exposure Science & Environmental Epidemiology*, 17(3):279–287.
- Freire C et al. (2010). Association of traffic-related air pollution with cognitive development in children. *Journal of Epidemiology and Community Health*, 64(3):223–228.
- Friedman MS et al. (2001). Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. *Journal of the American Medical Association*, 285(7):897–905.
- Fromme H et al. (2008). Chemical and morphological properties of particulate matter (PM₁₀, PM_{2.5}) in school classrooms and outdoor air. *Atmospheric Environment*, 42(27):6597–6605.
- Frye C et al. (2003). Association of lung function with declining ambient air pollution. *Environmental Health Perspectives*, 111(3):383–387.
- Fuks K et al. (2011). Long-term urban particulate air pollution, traffic noise, and arterial blood pressure. *Environmental Health Perspectives*, 119(12):1706–1711.
- Gallagher CM, Kovach JS, Meliker JR (2008). Urinary cadmium and osteoporosis in U.S. Women \geq 50 years of age: NHANES 1988–1994 and 1999–2004. *Environmental Health Perspectives*, 116(10):1338–1343.
- Gallo V et al. (2008). Validation of biomarkers for the study of environmental carcinogens: a review. *Biomarkers*, 13(5):505–534.
- Gan WQ et al. (2010). Changes in residential proximity to road traffic and the risk of death from coronary heart disease. *Epidemiology*, 21(5):642–649.
- Gan WQ et al. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environmental Health Perspectives*, 119(4):501–507.
- Gan WQ et al. (2012). Association of long-term exposure to community noise and traffic-related air pollution with coronary heart disease mortality. *American Journal of Epidemiology*, 175(9):898–906.
- Gariazzo C et al. (2011). Integrated model for the estimation of annual, seasonal, and episode PM₁₀ exposures of children in Rome, Italy. *Air Quality, Atmosphere & Health*, 4(3–4):169–178.
- Gauderman WJ et al. (2002). Association between air pollution and lung function growth in Southern California children: results from a second cohort. *American Journal of Respiratory and Critical Care Medicine*, 166(1):76–84.

- Gauderman WJ et al. (2004). The effect of air pollution on lung development from 10 to 18 years of age. *New England Journal of Medicine*, 351(11):1057–1067.
- Gauderman WJ et al. (2005). Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology*, 16(6):737–743.
- Gauderman WJ et al. (2007). Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet*, 369(9561):571–577.
- Gehring U et al. (2006). Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. *Epidemiology*, 17(5):545–551.
- Gehring U et al. (2010). Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *American Journal of Respiratory and Critical Care Medicine*, 181(6):596–603.
- Geiser M, Kreyling WG (2010). Deposition and biokinetics of inhaled nanoparticles. *Particle and Fibre Toxicology*, 7:2.
- Généreux M et al. (2008). Neighbourhood socioeconomic status, maternal education and adverse birth outcomes among mothers living near highways. *Journal of Epidemiology and Community Health*, 62(8):695–700.
- Gent JF et al. (2009). Symptoms and medication use in children with asthma and traffic-related sources of fine particle pollution. *Environmental Health Perspectives*, 117(7):1168–1174.
- Gentner DR et al. (2012). Elucidating secondary organic aerosol from diesel and gasoline vehicles through detailed characterization of organic carbon emissions. *Proceedings of the National Academy of Sciences of the United States of America*, 109(45):18318–18323.
- Gerlofs-Nijland ME et al. (2007). Toxicity of coarse and fine particulate matter from sites with contrasting traffic profiles. *Inhalation Toxicology*, 19(13):1055–1069.
- Geyh AS et al. (2000). The Harvard Southern California Chronic Ozone Exposure Study: assessing ozone exposure of grade-school-age children in two Southern California communities. *Environmental Health Perspectives*, 108(3):265–270.
- Ghio AJ et al. (1999). Sulfate content correlates with iron concentrations in ambient air pollution particles. *Inhalation Toxicology*, 11(4):293–307.
- Gilbert NL et al. (2003). Ambient nitrogen dioxide and distance from a major highway. *Science of the Total Environment*, 312(1–3):43–46.

- Gilbreath S, Yap P (2008). The potential impact of residential wood burning regulations in a California region: concurrent wintertime reductions in ambient pollution and cardiovascular mortality. *Epidemiology*, 19(6):S252.
- Gilmour MI et al. (2007). Comparative toxicity of size-fractionated airborne particulate matter obtained from different cities in the United States. *Inhalation Toxicology*, 19(Suppl. 1):7–16.
- Gilmour PS et al. (2006). Systemic imbalance of essential metals and cardiac gene expression in rats following acute pulmonary zinc exposure. *Journal of Toxicology and Environmental Health, Part A*, 69(22):2011–2032.
- Giovannini M et al. (2010). Hospital admissions for respiratory conditions in children and outdoor air pollution in Southwest Milan, Italy. *Acta Paediatrica*, 99(8):1180–1185.
- Godleski JJ et al. (2011). Toxicological evaluation of realistic emission source aerosols (TERESA): summary and conclusions. *Inhalation Toxicology*, 23(Suppl. 2):95–103.
- Goldberg MS et al. (2008). A panel study in congestive heart failure to estimate the short-term effects from personal factors and environmental conditions on oxygen saturation and pulse rate. *Occupational and Environmental Medicine*, 65(10):659–666.
- Gomes EC et al. (2011). Effect of vitamin supplementation on lung injury and running performance in a hot, humid, and ozone-polluted environment. *Scandinavian Journal of Medicine & Science in Sports*, 21(6):e452–e460.
- Gong H Jr et al. (2005). Respiratory responses to exposures with fine particulates and nitrogen dioxide in the elderly with and without COPD. *Inhalation Toxicology*, 17(3):123–132.
- Gonzalez-Pina R et al. (2008). Prenatal exposure to ozone disrupts cerebellar monoamine contents in newborn rats. *Neurochemical Research*, 33(5):912–918.
- Goodman JE et al. (2009). Meta-analysis of nitrogen dioxide exposure and airway hyper-responsiveness in asthmatics. *Critical Reviews in Toxicology*, 39(9):719–742.
- Goodman PG et al. (2009). Effect of air pollution controls on black smoke and sulfur dioxide concentrations across Ireland. *Journal of the Air & Waste Management Association*, 59(2):207–213.
- Gordian ME, Haneuse S, Wakefield J (2006). An investigation of the association between traffic exposure and the diagnosis of asthma in children. *Journal of Exposure Science & Environmental Epidemiology*, 16(1):49–55.

- Götschi T et al. (2008). Long-term effects of ambient air pollution on lung function: a review. *Epidemiology*, 19(5):690–701.
- Gottipolu RR et al. (2008). Cardiopulmonary responses of intratracheally instilled tire particles and constituent metal components. *Inhalation Toxicology*, 20(5):473–484.
- Gowers AM et al. (2012). Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. *Respirology*, 17(6):887–898.
- Graff DW et al. (2009). Exposure to concentrated coarse air pollution particles causes mild cardiopulmonary effects in healthy young adults. *Environmental Health Perspectives*, 117(7):1089–1094.
- Graham JA et al. (1987). Influence of exposure patterns of nitrogen dioxide and modifications by ozone on susceptibility to bacterial infectious disease in mice. *Journal of Toxicology and Environmental Health*, 21(1–2):113–125.
- Granados-Canal DJ et al. (2005). Air pollution and respiratory hospital admissions in greater Paris: exploring sex differences. *Archives of Environmental & Occupational Health*, 60(6):307–313.
- Grass DS et al. (2010). Airborne particulate metals in the New York City subway: a pilot study to assess the potential for health impacts. *Environmental Research*, 110(1):1–11.
- Grimsrud TK et al. (2002). Exposure to different forms of nickel and risk of lung cancer. *American Journal of Epidemiology*, 156(12):1123–1132.
- Grimsrud TK et al. (2003). Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. *Journal of Environmental Monitoring*, 5(2):190–197.
- Gruzieva O et al. (2012). Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *Journal of Allergy and Clinical Immunology*, 129(1):240–246.
- Gruzieva O et al. (2013). Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology*, 24(1):54–61.
- Gryparis A et al. (2004). Acute effects of ozone on mortality from the ‘air pollution and health: a European approach’ project. *American Journal of Respiratory and Critical Care Medicine*, 170(10):1080–1087.
- Guevara-Guzmán R et al. (2009). Estradiol prevents ozone-induced increases in brain lipid peroxidation and impaired social recognition memory in female rats. *Neuroscience*, 159(3):940–950.

- Gunaydin H, Houk KN (2009). Mechanisms of peroxyxynitrite-mediated nitration of tyrosine. *Chemical Research in Toxicology*, 22(5):894–898.
- Gustafson P, Ostman C, Sällsten G (2008). Indoor levels of polycyclic aromatic hydrocarbons in homes with or without wood burning for heating. *Environmental Science & Technology*, 42(14):5074–5080.
- Güven A et al. (2008). Alterations in semen parameters of toll collectors working at motorways: does diesel exposure induce detrimental effects on semen? *Andrologia*, 40(6):346–351.
- Guxens M, Sunyer J (2012). A review of epidemiological studies on neuropsychological effects of air pollution. *Swiss Medical Weekly*, 141:w13322.
- Hajat S et al. (2007). Outdoor air pollution and infant mortality: analysis of daily time-series data in 10 English cities. *Journal of Epidemiology and Community Health*, 61(8):719–722.
- Halatek T et al. (2011). The inflammatory response in lungs of rats exposed on the airborne particles collected during different seasons in four European cities. *Journal of Environmental Science and Health. Part A*, 46(13):1469–1481.
- Hall JV, Brajer V, Lurmann FW (2008). Measuring the gains from improved air quality in the San Joaquin Valley. *Journal of Environmental Management*, 88(4):1003–1015.
- Hallberg LM et al. (2012). *Part 3. Assessment of genotoxicity and oxidative stress after exposure to diesel exhaust from US-2007-compliant diesel engines: report on 1- and 3-month exposures in the ACES bioassay*. Boston, Health Effects Institute (Research Report 166; <http://pubs.healtheffects.org/getfile.php?u=709>, accessed 17 March 2013):121–158.
- Halonen JI et al. (2008). Urban air pollution, and asthma and COPD hospital emergency room visits. *Thorax*, 63(7):635–641.
- Halonen JI et al. (2009). Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. *Epidemiology*, 20(1):143–153.
- Haney JT Jr et al. (2012). Development of a unit risk factor for nickel and inorganic nickel compounds based on an updated carcinogenic toxicity assessment. *Regulatory Toxicology and Pharmacology*, 62(1):191–201.
- Hänninen OO et al. (2004a). Infiltration of ambient PM_{2.5} and levels of indoor generated non-ETS PM_{2.5} in residences of four European cities. *Atmospheric Environment*, 38(37):6411–6423.

- Hänninen OO et al. (2004b). The EXPOLIS study: implications for exposure research and environmental policy in Europe. *Journal of Exposure Analysis and Environmental Epidemiology*, 14(6):440–456.
- Hänninen OO et al. (2005). Reduction potential of urban PM_{2.5} mortality risk using modern ventilation systems in buildings. *Indoor Air*, 15(4):246–256.
- Hänninen OO et al. (2011). Seasonal patterns of outdoor PM infiltration into indoor environments: review and meta-analysis of available studies from different climatological zones in Europe. *Air Quality, Atmosphere & Health*, 4(3-4):221–233.
- Hansen C et al. (2010). The effect of ambient air pollution on sperm quality. *Environmental Health Perspectives*, 118(2):203–209.
- Happo MS et al. (2010). Inflammation and tissue damage in mouse lung by single and repeated dosing of urban air coarse and fine particles collected from six European cities. *Inhalation Toxicology*, 22(5):402–416.
- Harder V et al. (2005). Cardiovascular responses in unrestrained WKY rats to inhaled ultrafine carbon particles. *Inhalation Toxicology*, 17(1):29–42.
- Harrison RM, Beddows DCS, Dall’Osto M (2011). PMF analysis of wide-range particle size spectra collected on a major highway. *Environmental Science & Technology*, 45(13):5522–5528.
- Hart JE et al. (2011). Long-term ambient multipollutant exposures and mortality. *American Journal of Respiratory and Critical Care Medicine*, 183(1):73–78.
- Hedley AJ et al. (2002). Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet*, 360(9346):1646–1652.
- Hedley AJ et al. (2006). *Air pollution: costs and paths to a solution*. Hong Kong, Civic Exchange.
- Hedley AJ et al. (2008). Air pollution: costs and paths to a solution in Hong Kong – understanding the connections among visibility, air pollution, and health costs in pursuit of accountability, environmental justice, and health protection. *Journal of Toxicology and Environmental Health, Part A*, 71(9–10):544–554.
- HEI (2003). *Revised analyses of time-series studies of air pollution and health*. Boston, Health Effects Institute (<http://pubs.healtheffects.org/getfile.php?u=21>, accessed 29 March 2013).

- HEI (2004). *Health effects of outdoor air pollution in developing countries of Asia: a literature review*. Boston, Health Effects Institute (Special Report 15; <http://pubs.healtheffects.org/getfile.php?u=13>, accessed 29 March 2013).
- HEI (2010). *Public health and air pollution in Asia (PAPA): coordinated studies of short-term exposure to air pollution and daily mortality in four cities*. Boston, Health Effects Institute (Research Report 154; <http://pubs.healtheffects.org/view.php?id=348>, accessed 14 March 2013).
- HEI (2011). *Public health and air pollution in Asia (PAPA): coordinated studies of short-term exposure to air pollution and daily mortality in two Indian cities*. Boston, Health Effects Institute (Research Report 157; <http://pubs.healtheffects.org/getfile.php?u=623>, accessed 14 March 2013).
- HEI (2012). *Advanced Collaborative Emissions Study (ACES) subchronic exposure results: biologic responses in rats and mice and assessment of genotoxicity. Part 2*. Boston, Health Effects Institute (Research Report 166; <http://pubs.healtheffects.org/getfile.php?u=709>, accessed 10 April 2013).
- HEI Panel on the Health Effects of Traffic-Related Air Pollution (2010). *Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects*. Boston, Health Effects Institute (Special Report 17; <http://pubs.healtheffects.org/getfile.php?u=553>, accessed 14 March 2013).
- Heidenfelder BL et al. (2009). Comparative microarray analysis and pulmonary changes in Brown Norway rats exposed to ovalbumin and concentrated air particulates. *Toxicological Sciences*, 108(1):207–221.
- Heinrich J, Hoelscher B, Wichmann HE (2000). Decline of ambient air pollution and respiratory symptoms in children. *American Journal of Respiratory and Critical Care Medicine*, 161(6):1930–1936.
- Heinrich J et al. (2013). Long-term exposure to NO₂ and PM₁₀ and all-cause and cause-specific mortality in a prospective cohort of women. *Occupational and Environmental Medicine*, 70(3):179–186.
- Helleday R et al. (1995). Nitrogen dioxide exposure impairs the frequency of the mucociliary activity in healthy subjects. *European Respiratory Journal*, 8(10):1664–1668.
- Henderson SB et al. (2011). Three measures of forest fire smoke exposure and their associations with respiratory and cardiovascular health outcomes in a population-based cohort. *Environmental Health Perspectives*, 119(9):1266–1271.
- Henschel S et al. (2012). Air pollution interventions and their impact on public health. *International Journal of Public Health*, 57(5):757–768.

- Hernandez ML et al. (2010). Atopic asthmatic subjects but not atopic subjects without asthma have enhanced inflammatory response to ozone. *Journal of Allergy and Clinical Immunology*, 126(3):537–544.e1.
- Herner JD et al. (2011). Effect of advanced aftertreatment for PM and NO_x reduction on heavy-duty diesel engine ultrafine particle emissions. *Environmental Science & Technology*, 45(6):2413–2419.
- Hesterberg TW et al. (2009). Critical review of the human data on short-term nitrogen dioxide (NO₂) exposures: evidence for NO₂ no-effect levels. *Critical Reviews in Toxicology*, 39(9):743–781.
- Hildebrandt K et al. (2009). Short-term effects of air pollution: a panel study of blood markers in patients with chronic pulmonary disease. *Particle and Fibre Toxicology*, 6:25.
- Hitchins J et al. (2000). Concentrations of submicrometre particles from vehicle emissions near a major road. *Atmospheric Environment*, 34(1):51–59.
- Hodgkins SR et al. (2010). NO₂ inhalation induces maturation of pulmonary CD11c+ cells that promote antigen-specific CD4+ T cell polarization. *Respiratory Research*, 11:102.
- Hoek G et al. (1997). Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, The Netherlands. *Archives of Environmental Health*, 52(6):455–463.
- Hoek G et al. (2002a). Spatial variability of fine particle concentrations in three European areas. *Atmospheric Environment*, 36(25):4077–4088.
- Hoek G et al. (2002b). Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet*, 360(9341):1203–1209.
- Hoek G et al. (2010). Concentration response functions for ultrafine particles and all-cause mortality and hospital admissions: results of a European expert panel elicitation. *Environmental Science & Technology*, 44(1):476–482.
- Hoek G et al. (2012). PM₁₀, and children's respiratory symptoms and lung function in the PATY study. *European Respiratory Journal*, 40(3):538–547.
- Hoffmann B et al. (2006). Residence close to high traffic and prevalence of coronary heart disease. *European Heart Journal*, 27(22):2696–2702.
- Hoffmann B et al. (2007). Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation*, 116(5):489–496.

- Holstius DM et al. (2012). Birth weight following pregnancy during the 2003 Southern California wildfires. *Environmental Health Perspectives*, 120(9):1340–1345.
- Hou Q et al. (2010). An evaluation of resident exposure to respirable particulate matter and health economic loss in Beijing during Beijing 2008 Olympic Games. *Science of the Total Environment*, 408(19):4026–4032.
- Hu W et al. (2008). Temperature, air pollution and total mortality during summers in Sydney, 1994–2004. *International Journal of Biometeorology*, 52(7):689–696.
- Huang W et al. (2009). Changes in heart rate variability in the cardiovascular elderly Beijing residents during the Beijing Olympics. *ISEE Annual Conference, Dublin, 25–29 August 2009*.
- Huang W et al. (2012). Inflammatory and oxidative stress responses of healthy young adults to changes in air quality during the Beijing Olympics. *American Journal of Respiratory and Critical Care Medicine*, 186(11):1150–1159.
- Hurley F et al. (2005). *Methodology for the cost-benefit analysis for CAFE. Volume 2: health impact assessment*. Didcot, AEA Technology (AEAT/ED51014/Methodology Volume 2: Issue 2; http://ec.europa.eu/environment/archives/cape/pdf/cba_methodology_vol2.pdf, accessed 14 March 2013.).
- Hyde D et al. (1978). Morphometric and morphologic evaluation of pulmonary lesions in Beagle dogs chronically exposed to high ambient levels of air pollutants. *Laboratory Investigation*, 38(4):455–469.
- IARC (2010). *Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures*. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 92; <http://monographs.iarc.fr/ENG/Monographs/vol92/mono92.pdf>, accessed 29 March 2013).
- IARC (2012). *A review of human carcinogens: arsenic, metals, fibres, and dusts*. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 100C; <http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php>, accessed 28 March 2013).
- Ichinose T, Fujii K, Sagai M (1991). Experimental studies on tumor promotion by nitrogen dioxide. *Toxicology*, 67(2):211–225.
- ICRP (1994). Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection (ICRP). *Annals of the ICRP*, 24(1–3):1–482.

- Ilacqua V, Jantunen MJ (2003). Contributions of outdoor, indoor and other sources to personal VOC exposure in five European cities. In: Sekhar C, Cheong D, eds. *Healthy Buildings 2003: energy-efficient healthy buildings. Proceedings of ISIAQ 7th International Conference, 7–11 December 2003, Singapore, Vol. 1*. Singapore, National University of Singapore:427–433.
- Inoue K et al. (2008). Role of metallothionein in lung inflammation induced by ozone exposure in mice. *Free Radical Biology & Medicine*, 45(12):1714–1722.
- Iqbal ZM, Dahl K, Epstein SS (1981). Biosynthesis of dimethylnitrosamine in dimethylamine-treated mice after exposure to nitrogen dioxide. *Journal of the National Cancer Institute*, 67(1):137–141.
- Ishigami A et al. (2008). Volcanic sulfur dioxide and acute respiratory symptoms on Miyakejima Island. *Occupational and Environmental Medicine*, 65(10):701–707.
- Iskandar A et al. (2012). Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. *Thorax*, 67(3):252–257.
- Islam T et al. (2008). Ozone, oxidant defense genes, and risk of asthma during adolescence. *American Journal of Respiratory and Critical Care Medicine*, 177(4):388–395.
- Islam T et al. (2009). Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax*, 64(3):197–202.
- Ito K, De Leon SF, Lippmann M (2005). Associations between ozone and daily mortality: analysis and meta-analysis. *Epidemiology*, 16(4):446–457.
- Ito K, Thurston GD, Silverman RA (2007). Characterization of PM_{2.5}, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. *Journal of Exposure Science & Environmental Epidemiology*, 17(Suppl. 2):S45–S60.
- Ito K et al. (2006). PM source apportionment and health effects: 2. An investigation of intermethod variability in associations between source-apportioned fine particle mass and daily mortality in Washington, DC. *Journal of Exposure Science & Environmental Epidemiology*, 16(4):300–310.
- Ito K et al. (2011). Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environmental Health Perspectives*, 119(4):467–473.
- Iwasawa S et al. (2009). Effects of SO₂ on respiratory system of adult Miyakejima resident 2 years after returning to the island. *Journal of Occupational Health*, 51(1):38–47.

- Jacobs L et al. (2010). Subclinical responses in healthy cyclists briefly exposed to traffic-related air pollution: an intervention study. *Environmental Health*, 9:64.
- Jacobs L et al. (2012). Acute changes in pulse pressure in relation to constituents of particulate air pollution in elderly persons. *Environmental Research*, 117:60–67.
- Jacobson L da SV et al. (2012). Association between fine particulate matter and the peak expiratory flow of schoolchildren in the Brazilian subequatorial Amazon: a panel study. *Environmental Research*, 117:27–35.
- Jacquemin B et al. (2009). Source category-specific PM_{2.5} and urinary levels of Clara cell protein CC16. The ULTRA study. *Inhalation Toxicology*, 21(13):1068–1076.
- Jacquemin B et al. (2012). Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma. *Journal of Epidemiology and Community Health*, 66(9):796–802.
- Jalaludin B et al. (2006). Associations between ambient air pollution and daily emergency department attendances for cardiovascular disease in the elderly (65+ years), Sydney, Australia. *Journal of Exposure Science & Environmental Epidemiology*, 16(3):225–237.
- Jalaludin B et al. (2007). Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia. *Environmental Health*, 6:16.
- Jalaludin B et al. (2008). Air pollution and ED visits for asthma in Australian children: a case-crossover analysis. *International Archives of Occupational and Environmental Health*, 81(8):967–974.
- Jalava PI et al. (2008). Effects of solubility of urban air fine and coarse particles on cytotoxic and inflammatory responses in RAW 264.7 macrophage cell line. *Toxicology and Applied Pharmacology*, 229(2):146–160.
- Jalava PI et al. (2010). Toxicological effects of emission particles from fossil- and biodiesel-fueled diesel engine with and without DOC/POC catalytic converter. *Inhalation Toxicology*, 22(Suppl. 2):48–58.
- Jang M, Ghio AJ, Cao G (2006). Exposure of BEAS-2B cells to secondary organic aerosol coated on magnetic nanoparticles. *Chemical Research in Toxicology*, 19(8):1044–1050.
- Janssen NAH et al. (2011). Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM₁₀ and PM_{2.5}. *Environmental Health Perspectives*, 119(12):1691–1699.

- Janssen NAH et al. (2012). *Health effects of black carbon*. Copenhagen, WHO Regional Office for Europe
(http://www.euro.who.int/__data/assets/pdf_file/0004/162535/e96541.pdf, accessed 7 May 2013).
- Jantunen MJ et al. (1999). *Final report: air pollution exposure in European cities: the EXPOLIS study*. Helsinki, National Public Health Institute
(Kansanterveyslaitoksen julkaisu B16/1999).
- Jayaraman-Nidhi G (2008). Air pollution and associated respiratory morbidity in Delhi. *Health Care Management Science*, 11(2):132–138.
- JECFA (2011). *Safety evaluation of certain food additives and contaminants*. Geneva, World Health Organization and Food and Agriculture Organization of the United Nations (WHO Food Additives Series: 64;
http://whqlibdoc.who.int/publications/2011/9789241660648_eng.pdf, accessed 22 March 2013).
- Jedlińska-Krakowska M et al. (2006). The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. *Polish Journal of Veterinary Sciences*, 9(1):11–16.
- Jerrett M et al. (2004). Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. *Journal of Epidemiology and Community Health*, 58(1):31–40.
- Jerrett M et al. (2005). Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology*, 16(6):727–736.
- Jerrett M et al. (2007). Modeling the intraurban variability of ambient traffic pollution in Toronto, Canada. *Journal of Toxicology and Environmental Health, Part A*, 70(3–4):200–212.
- Jerrett M et al. (2009a). Long-term ozone exposure and mortality. *New England Journal of Medicine*, 360(11):1085–1095.
- Jerrett M et al. (2009b). A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. *Environmental Health Perspectives*, 117(5):772–777.
- Jerrett M et al. (2011). *Spatiotemporal analysis of air pollution and mortality in California based on the American Cancer Society Cohort: final report*. Sacramento, State of California Air Resources Board Research Division
(<http://www.arb.ca.gov/research/apr/past/06-332.pdf>, accessed 22 March 2013).

- Ji M, Cohan DS, Bell ML (2011). Meta-analysis of the association between short-term exposure to ambient ozone and respiratory hospital admissions. *Environmental Research Letters*, 6(2): 024006.
- Jia C, Batterman S (2010). A critical review of naphthalene sources and exposures relevant to indoor and outdoor air. *International Journal of Environmental Research and Public Health*, 7(7):2903–2939.
- Jia Y et al. (2011). Estimated reduction in cancer risk due to PAH exposures if source control measures during the 2008 Beijing Olympics were sustained. *Environmental Health Perspectives*, 119(6):815–820.
- Jiang LL et al. (2007). A time series analysis of outdoor air pollution and preterm birth in Shanghai, China. *Biomedical and Environmental Sciences*, 20(5):426–431.
- Jiménez E et al. (2010). Role of Saharan dust in the relationship between particulate matter and short-term daily mortality among the elderly in Madrid (Spain). *Science of the Total Environment*, 408(23):5729–5736.
- Jimenez JL et al. (2009). Evolution of organic aerosols in the atmosphere. *Science*, 326(5959):1525–1529.
- Johannesson S et al. (2007). Exposure to fine particles (PM_{2.5} and PM₁) and black smoke in the general population: personal, indoor, and outdoor levels. *Journal of Exposure Science & Environmental Epidemiology*, 17(7):613–624.
- Johansson C, Burman L, Forsberg B (2009). The effects of congestions tax on air quality and health. *Atmospheric Environment*, 43(31):4843–4854.
- Johns DO, Linn WS (2011). A review of controlled human SO₂ exposure studies contributing to the US EPA integrated science assessment for sulfur oxides. *Inhalation Toxicology*, 23(1):33–43.
- Johns DO, Svendsgaard D, Linn WS (2010). Analysis of the concentration-respiratory response among asthmatics following controlled short-term exposures to sulfur dioxide. *Inhalation Toxicology*, 22(14):1184–1193.
- Johnston FH et al. (2013). Evaluation of interventions to reduce air pollution from biomass smoke on mortality in Launceston, Australia: retrospective analysis of daily mortality, 1994–2007. *British Medical Journal*, 346 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3541469/>, accessed 26 February 2013).
- Jones AM et al. (2012). A large reduction in airborne particle number concentrations at the time of the introduction of ‘sulphur free’ diesel and the London Low Emission Zone. *Atmospheric Environment*, 50:129–138.

- Jones SR et al. (2007). Lung cancer mortality at a UK tin smelter. *Occupational Medicine*, 57(4):238–245.
- Jörres R et al. (1995). The effect of 1 ppm nitrogen dioxide on bronchoalveolar lavage cells and inflammatory mediators in normal and asthmatic subjects. *European Respiratory Journal*, 8(3):416–424.
- Kajekar R et al. (2007). Early postnatal exposure to allergen and ozone leads to hyperinnervation of the pulmonary epithelium. *Respiratory Physiology & Neurobiology*, 155(1):55–63.
- Kan H, Jia J, Chen B (2004a). [A times-series study on the association of stroke mortality and air pollution in Zhabei District, Shanghai]. *Wei Sheng Yan Jiu [Journal of Hygiene Research]*, 33(1):36–38 (in Chinese).
- Kan H, Jia J, Chen B (2004b). The association of daily diabetes mortality and outdoor air pollution in Shanghai, China. *Journal of Environmental Health*, 67(3):21–26.
- Kan H et al. (2007). Traffic exposure and lung function in adults: the Atherosclerosis Risk in Communities study. *Thorax*, 62(10):873-879.
- Karanasiou A et al. (2012). Health effects from Sahara dust episodes in Europe: literature review and research gaps. *Environment International*, 47:107–114.
- Karner AA, Eisinger DS, Niemeier DA (2010). Near-roadway air quality: synthesizing the findings from real-world data. *Environmental Science & Technology*, 44(14):5334–5344.
- Karr CJ et al. (2007). Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. *American Journal of Epidemiology*, 165(5):553–560.
- Karr CJ et al. (2009a). Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. *Environmental Research*, 109(3):321–327.
- Karr CJ et al. (2009b). Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. *American Journal of Respiratory and Critical Care Medicine*, 180(10):995–1001.
- Katsouyanni K et al. (1997). Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Air Pollution and Health: a European Approach. *British Medical Journal (Clinical Research Edition)*, 314(7095):1658–1663.

- Katsouyanni K et al. (2001). Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology*, 12(5):521–531.
- Katsouyanni K et al. (2009). *Air pollution and health: a European and North American approach (APHENA)*. Boston, Health Effects Institute, (Research Report 142; <http://pubs.healtheffects.org/getfile.php?u=518>, accessed 14 March 2013).
- Kaur S, Nieuwenhuijsen MJ, Colville RN (2007). Fine particulate matter and carbon monoxide exposure concentrations in urban street transport microenvironments. *Atmospheric Environment*, 41(23):4781–4810.
- Kavlock R, Daston G, Grabowski CT (1979). Studies on the developmental toxicity of ozone. I. Prenatal effects. *Toxicology and Applied Pharmacology*, 48(1 Pt 1):19–28.
- Kavlock RJ, Meyer E, Grabowski CT (1980). Studies on the developmental toxicity of ozone: postnatal effects. *Toxicology Letters*, 5(1):3–9.
- Kelly FJ (2003). Oxidative stress: its role in air pollution and adverse health effects. *Occupational and Environmental Medicine*, 60(8):612–616.
- Kelly FJ, Tetley TD (1997). Nitrogen dioxide depletes uric acid and ascorbic acid but not glutathione from lung lining fluid. *Biochemical Journal*, 325(Pt 1):95–99.
- Kelly FJ et al. (2011). *The impact of the congestion charging scheme on air quality in London. Part 1. Emissions modeling and analysis of air pollution measurements*. Boston, Health Effects Institute (Research Report 155; <http://pubs.healtheffects.org/getfile.php?u=638>, accessed 17 March 2013):5–71.
- Keuken MP et al. (2010). Reduced NO_x and PM₁₀ emissions on urban motorways in the Netherlands by 80 km/h speed management. *Science of the Total Environment*, 408(12):2517–2526.
- Keuken MP et al. (2012). Trends in primary NO₂ and exhaust PM emissions from road traffic for the period 2000–2020 and implications for air quality and health in the Netherlands. *Atmospheric Environment*, 54:313–319.
- Kim CS et al. (2011). Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *American Journal of Respiratory and Critical Care Medicine*, 183(9):1215–1221.
- Kim JJ et al. (2004). Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *American Journal of Respiratory and Critical Care Medicine*, 170(5):520–526.

- Kim JJ et al. (2008). Residential traffic and children's respiratory health. *Environmental Health Perspectives*, 116(9):1274–1279.
- Kim JY et al. (2007). Panel discussion review: session two – interpretation of observed associations between multiple ambient air pollutants and health effects in epidemiologic analyses. *Journal of Exposure Science & Environmental Epidemiology*, 17(Suppl. 2):S83–S89.
- Kim SY, Kim H, Kim J (2006). [Effects of air pollution on asthma in Seoul: comparisons across subject characteristics]. *Yebang Ŭihakhoe chi [Journal of Preventive Medicine and Public Health]*, 39(4):309–316 (in Korean).
- Kim SY et al. (2004). Determining the threshold effect of ozone on daily mortality: an analysis of ozone and mortality in Seoul, Korea, 1995–1999. *Environmental Research*, 94(2):113–119.
- Kim SY et al. (2012). The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. *Environmental Health Perspectives*, 120(8):1094–1099.
- Kinney PL, Thurston GD, Raizenne M (1996). The effects of ambient ozone on lung function in children: a reanalysis of six summer camp studies. *Environmental Health Perspectives*, 104(2):170–174.
- Kleinman MT et al. (2003). Toxicity of chemical components of fine particles inhaled by aged rats: effects of concentration. *Journal of the Air & Waste Management Association*, 53(9):1080–1087.
- Kleinman MT et al. (2007). Inhalation of concentrated ambient particulate matter near a heavily trafficked road stimulates antigen-induced airway responses in mice. *Inhalation Toxicology*, 19(Suppl. 1):117–126.
- Kleinman MT et al. (2008). Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways. *Toxicology Letters*, 178(2):127–130.
- Kloog I et al. (2012). Acute and chronic effects of particles on hospital admissions in New-England. *PloS ONE*, 7(4):e34664.
- Knol AB et al. (2009). Expert elicitation on ultrafine particles: likelihood of health effects and causal pathways. *Particle and Fibre Toxicology*, 6:19.
- Ko FWS et al. (2007). Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. *Clinical and Experimental Allergy*, 37(9):1312–1319.
- Kodavanti UP et al. (2011). Vascular and cardiac impairments in rats inhaling ozone and diesel exhaust particles. *Environmental Health Perspectives*, 119(3):312–318.

- Koehler C et al. (2011). Ex vivo toxicity of nitrogen dioxide in human nasal epithelium at the WHO defined 1-h limit value. *Toxicology Letters*, 207(1):89–95.
- Koistinen KJ et al. (2004). Sources of fine particulate matter in personal exposures and residential indoor, residential outdoor and workplace microenvironments in the Helsinki phase of the EXPOLIS study. *Scandinavian Journal of Work, Environment & Health*, 30(Suppl. 2):36–46.
- Komarnicki GJK (2005). Lead and cadmium in indoor air and the urban environment. *Environmental Pollution*, 136(1):47–61.
- Koop G, Tole L (2004). Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? *Journal of Environmental Economics and Management*, 47(1):30–54.
- Kornartit C et al. (2010). Activity pattern and personal exposure to nitrogen dioxide in indoor and outdoor microenvironments. *Environment International*, 36(1):36–45.
- Kotzias D et al. (2009). Exposure to multiple air contaminants in public buildings, schools and kindergartens – the European Indoor Air Monitoring and Exposure Assessment (AIRMEX) study. *Fresenius Environmental Bulletin*, 18(5a):670–681.
- Kousa A et al. (2001). Personal exposures to NO₂ in the EXPOLIS-study: relation to residential indoor, outdoor and workplace concentrations in Basel, Helsinki and Prague. *Atmospheric Environment*, 35(20):3405–3412.
- Kovats RS, Hajat S (2008). Heat stress and public health: a critical review. *Annual Review of Public Health*, 29:41–55.
- Kowalska M et al. (2008). Air pollution and daily mortality in urban Katowice, 1994–95 and 2001–02. *Polish Journal of Environmental Studies*, 17(5):733–738.
- Krämer U et al. (1999). Airway diseases and allergies in East and West German children during the first 5 years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. *International Journal of Epidemiology*, 28(5):865–873.
- Krämer U et al. (2010). Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. *Environmental Health Perspectives*, 118(9):1273–1279.
- Kraus U et al. (2011). Particle-associated organic compounds and symptoms in myocardial infarction survivors. *Inhalation Toxicology*, 23(7):431–447.

- Krewski D et al. (2000). *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality*. Boston, Health Effects Institute.
- Krewski D et al. (2004). Validation of the Harvard Six Cities Study of particulate air pollution and mortality. *New England Journal of Medicine*, 350(2):198–199.
- Krewski D et al. (2009). *Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality*. Boston, Health Effects Institute (Research Report 140; <http://pubs.healtheffects.org/getfile.php?u=478>, accessed 17 March 2013):5–114; commentary: 115–136.
- Kreyling WG, Hirn S, Schleh C (2010). Nanoparticles in the lung. *Nature Biotechnology*, 28(12):1275–1276.
- Kreyling WG et al. (2013). Differences in the biokinetics of inhaled nano- versus micrometer-sized particles. *Accounts of Chemical Research*, 46(3):714–722.
- Kubota K et al. (1987). Effects of long-term nitrogen dioxide exposure on rat lung: morphological observations. *Environmental Health Perspectives*, 73:157–169.
- Kulmala M, Kerminen VM (2008). On the formation and growth of atmospheric nanoparticles. *Atmospheric Research*, 90(2–4):132–150.
- Kumae T, Arakawa H (2006). Comparison of effects of in vivo nitrogen dioxide exposure starting from different periods on alveolar macrophage activity, assessed by a chemiluminescence technique in Brown-Norway rats. *Luminescence*, 21(4):226–232.
- Künzli N et al. (2005). Ambient air pollution and atherosclerosis in Los Angeles. *Environmental Health Perspectives*, 113(2):201–206.
- Künzli N et al. (2006). Comparison of oxidative properties, light absorbance, total and elemental mass concentration of ambient PM_{2.5} collected at 20 European sites. *Environmental Health Perspectives*, 114(5):684–690.
- Künzli N et al. (2008). An attributable risk model for exposures assumed to cause both chronic disease and its exacerbations. *Epidemiology*, 19(2):179–185.
- Künzli N et al. (2010). Ambient air pollution and the progression of atherosclerosis in adults. *PloS ONE*, 5(2):e9096.
- Kusha M et al. (2012). Controlled exposure study of air pollution and T-wave alternans in volunteers without cardiovascular disease. *Environmental Health Perspectives*, 120(8):1157–1161.

- Laden F et al. (2006). Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *American Journal of Respiratory and Critical Care Medicine*, 173(6):667–672.
- Lai H.K. et al. (2004). Personal exposures and microenvironment concentrations of PM_{2.5}, VOC, NO₂ and CO in Oxford, UK. *Atmospheric Environment*, 38(37):6399–6410.
- Lall R, Ito K, Thurston GD (2011). Distributed lag analyses of daily hospital admissions and source-apportioned fine particle air pollution. *Environmental Health Perspectives*, 119(4):455–460.
- Langlois PH et al. (2009). Maternal residential proximity to waste sites and industrial facilities and conotruncal heart defects in offspring. *Paediatric and Perinatal Epidemiology*, 23(4):321–331.
- Langrish JP et al. (2009). Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Particle and Fibre Toxicology*, 6:8.
- Langrish JP et al. (2010). Exposure to nitrogen dioxide is not associated with vascular dysfunction in man. *Inhalation Toxicology*, 22(3):192–198.
- Langrish JP et al. (2012). Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environmental Health Perspectives*, 120(3):367–372.
- Lanki T et al. (2006). Associations of traffic related air pollutants with hospitalisation for first acute myocardial infarction: the HEAPSS study. *Occupational and Environmental Medicine*, 63(12):844–851.
- Lanki T et al. (2007). Determinants of personal and indoor PM_{2.5} and absorbance among elderly subjects with coronary heart disease. *Journal of Exposure Science & Environmental Epidemiology*, 17(2):124–133.
- Lanphear BP et al. (2005). Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environmental Health Perspectives*, 113(7):894–899.
- Larrieu S et al. (2007). Short term effects of air pollution on hospitalizations for cardiovascular diseases in eight French cities: the PSAS program. *Science of the Total Environment*, 387(1-3):105–112.
- Larsson B-M et al. (2010). Limited airway effects in mild asthmatics after exposure to air pollution in a road tunnel. *Respiratory Medicine*, 104(12):1912–1918.

- Latzin P et al. (2009). Air pollution during pregnancy and lung function in newborns: a birth cohort study. *European Respiratory Journal*, 33(3):594–603.
- Lauby-Secretan B et al. (2011). Bitumens and bitumen emissions, and some heterocyclic polycyclic aromatic hydrocarbons. *Lancet Oncology*, 12(13):1190–1191.
- Laumbach RJ et al. (2010). Acute changes in heart rate variability in subjects with diabetes following a highway traffic exposure. *Journal of Occupational and Environmental Medicine*, 52(3):324–331.
- Layachi S et al. (2012). Effect of combined nitrogen dioxide and carbon nanoparticle exposure on lung function during ovalbumin sensitization in Brown Norway rat. *PLoS ONE*, 7(9):e45687.
- Lee DS, Garland JA, Fox AA (1994). Atmospheric concentrations of trace elements in urban areas of the United Kingdom. *Atmospheric Environment*, 28(16):2691–2713.
- Lee JT, Son JY, Cho YS (2007a). Benefits of mitigated ambient air quality due to transportation control on childhood asthma hospitalization during the 2002 summer Asian Games in Busan, Korea. *Journal of the Air & Waste Management Association*, 57(8):968–973.
- Lee JT, Son JY, Cho YS (2007b). A comparison of mortality related to urban air particles between periods with Asian dust days and without Asian dust days in Seoul, Korea, 2000–2004. *Environmental Research*, 105(3):409–413.
- Lee JT et al. (2000). Air pollution and daily mortality in seven major cities of Korea, 1991–1997. *Environmental Research*, 84(3):247–254.
- Lee K et al. (2002). Nitrous acid, nitrogen dioxide, and ozone concentrations in residential environments. *Environmental Health Perspectives*, 110(2):145–150.
- Lee PC et al. (2013). First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. *Maternal and Child Health Journal*, 17:545–555.
- Lee SL, Wong WHS, Lau YL (2006). Association between air pollution and asthma admission among children in Hong Kong. *Clinical and Experimental Allergy*, 36(9):1138–1146.
- Lee YL et al. (2003). Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. *European Respiratory Journal*, 21(6):964–970.
- Lee YL et al. (2012). Pulmonary function and incident bronchitis and asthma in children: a community-based prospective cohort study. *PLoS ONE*, 7(3):e32477.

- Leem JH et al. (1998). Short-term effects of air pollution on hospital visits for respiratory diseases in Seoul. *Korean Journal of Occupational and Environmental Medicine*, 10(3):333–342.
- Lefranc A et al. (2009). Pollution atmosphérique et maladies cardiovasculaires: éléments apportés par le programme de surveillance air et santé. *Archives des Maladies Professionnelles et de l'Environnement*, 70(3):339–345.
- Leitte AM et al. (2011). Size-segregated particle number concentrations and respiratory emergency room visits in Beijing, China. *Environmental Health Perspectives*, 119(4):508–513.
- Leitte AM et al. (2012). Associations between size-segregated particle number concentrations and respiratory mortality in Beijing, China. *International Journal of Environmental Health Research*, 22(2):119–133.
- Lepeule J et al. (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environmental Health Perspectives*, 120(7):965–970.
- Le Tertre A et al. (2002). Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. *Archives of Environmental Health*, 57(4):311–319.
- Lewné M et al. (2004). Spatial variation in nitrogen dioxide in three European areas. *Science of the Total Environment*, 332(1–3):217–230.
- Li H et al. (2011). Oxidative stress, endothelial dysfunction and inflammatory response in rat heart to NO₂ inhalation exposure. *Chemosphere*, 82(11):1589–1596.
- Li N et al. (2010). Ambient ultrafine particles provide a strong adjuvant effect in the secondary immune response: implication for traffic-related asthma flares. *American Journal of Physiology – Lung Cellular and Molecular Physiology*, 299(3):L374–L383.
- Li R, Meng Z, Xie J (2007). Effects of sulfur dioxide derivatives on four asthma-related gene expressions in human bronchial epithelial cells. *Toxicology Letters*, 175(1–3):71–81.
- Li R, Meng Z, Xie J (2008). Effects of sulfur dioxide on the expressions of EGF, EGFR, and COX-2 in airway of asthmatic rats. *Archives of Environmental Contamination and Toxicology*, 54(4):748–757.
- Li W et al. (2011). Internally mixed sea salt, soot, and sulfates at Macao, a coastal city in South China. *Journal of the Air & Waste Management Association*, 61(11):1166–1173.
- Li X et al. (2009). Amino acids and gaseous signaling. *Amino Acids*, 37(1):65–78.

- Li Y et al. (2010). Air quality and outpatient visits for asthma in adults during the 2008 Summer Olympic Games in Beijing. *Science of the Total Environment*, 408(5):1226–1227.
- Liao D et al. (2005). Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. *Journal of Exposure Analysis and Environmental Epidemiology*, 15(4):319–328.
- Lighthall D, Nunes D, Tyner T (2009). *Environmental health evaluation of Rule 4901: domestic wood burning – a case study of the Fresno/Clovis and Bakersfield metropolitan areas*. Fresno, CA, Central Valley Health Policy Institute (<http://www.fresnostate.edu/chhs/cvhipi/documents/wood-burning-report.pdf>, accessed 27 March 2013).
- Lim SS et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859):2224–2260.
- Lin S et al. (2002). Childhood asthma hospitalization and residential exposure to state route traffic. *Environmental Research*, 88(2):73–81.
- Lin S et al. (2008). Chronic exposure to ambient ozone and asthma hospital admissions among children. *Environmental Health Perspectives*, 116(12):1725–1730.
- Lin S et al. (2013). Impact of NO(x) emissions reduction policy on hospitalizations for respiratory disease in New York State. *Journal of Exposure Science & Environmental Epidemiology*, 23(1):73–80.
- Lin W et al. (2011). Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. *Environmental Health Perspectives*, 119(10):1507–1512.
- Linares C, Díaz J (2010). Short-term effect of concentrations of fine particulate matter on hospital admissions due to cardiovascular and respiratory causes among the over-75 age group in Madrid, Spain. *Public Health*, 124(1):28–36.
- Lipfert FW et al. (2006). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: long-term mortality in a cohort of US veterans. *Atmospheric Environment*, 40(1):154–169.
- Lippmann M, Chen LC (2009). Health effects of concentrated ambient air particulate matter (CAPs) and its components. *Critical Reviews in Toxicology*, 39(10):865–913.
- Lippmann M et al. (2006). Cardiovascular effects of nickel in ambient air. *Environmental Health Perspectives*, 114(11):1662–1669.

- Lipsett MJ et al. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *American Journal of Respiratory and Critical Care Medicine*, 184(7):828–835.
- Liu C et al. (2013). Epidemiological and experimental links between air pollution and type 2 diabetes. *Toxicologic Pathology*, 41(2):361–373.
- Liu L et al. (2009). Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. *Environmental Health Perspectives*, 117(4):668–674.
- Liu LJ, Delfino R, Koutrakis P (1997). Ozone exposure assessment in a Southern California community. *Environmental Health Perspectives*, 105(1):58–65.
- Liu LJ et al. (1995). Assessment of ozone exposures in the greater metropolitan Toronto area. *Journal of the Air & Waste Management Association*, 45(4):223–234.
- Ljungman PLS et al. (2008). Rapid effects of air pollution on ventricular arrhythmias. *European Heart Journal*, 29(23):2894–2901.
- London Air (2013). Statistical tools: my own choice of statistics [web site]. London, Environmental Research Group, King’s College London (<http://www.londonair.org.uk/london/asp/advstats.asp?advstats=Various&ratidate=>, accessed 27 March 2013).
- López I et al. (2008). Ultrastructural alterations during embryonic rats’ lung development caused by ozone. *Journal of Electron Microscopy*, 57(1):19–23.
- López-Villarrubia E et al. (2010) Air pollution and mortality in the Canary Islands: a time-series analysis. *Environmental Health*, 9(8).
- López-Villarrubia E et al. (2012). Characterizing mortality effects of particulate matter size fractions in the two capital cities of the Canary Islands. *Environmental Research*, 112:129–138.
- Lubin JH et al. (2008). Respiratory cancer and inhaled inorganic arsenic in copper smelters workers: a linear relationship with cumulative exposure that increases with concentration. *Environmental Health Perspectives*, 116(12):1661–1665.
- Luch A, ed. (2005). *The carcinogenic effects of polycyclic aromatic hydrocarbons*. London, Imperial College Press.
- Lucking AJ et al. (2011). Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. *Circulation*, 123(16):1721–1728.

- Lund AK et al. (2007). Gasoline exhaust emissions induce vascular remodeling pathways involved in atherosclerosis. *Toxicological Sciences*, 95(2):485–494.
- Lundberg JO, Weitzberg E (2010). NO-synthase independent NO generation in mammals. *Biochemical and Biophysical Research Communications*, 396(1):39–45.
- Lundberg JO, Weitzberg E, Gladwin MT (2008). The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nature Reviews Drug Discovery*, 7(2):156–167.
- Lundström NG et al. (2006). Lung cancer development in primary smelter workers: a nested case-referent study. *Journal of Occupational and Environmental Medicine*, 48(4):376–380.
- Ma L et al. (2008). Effects of airborne particulate matter on respiratory morbidity in asthmatic children. *Journal of Epidemiology*, 18(3):97–110.
- MacIntyre EA et al. (2011). Residential air pollution and otitis media during the first two years of life. *Epidemiology*, 22(1):81–89.
- Madden MC et al. (2000). Effect of ozone on diesel exhaust particle toxicity in rat lung. *Toxicology and Applied Pharmacology*, 168(2):140–148.
- Malig BJ, Ostro BD (2009). Coarse particles and mortality: evidence from a multi-city study in California. *Occupational and Environmental Medicine*, 66(12):832–839.
- Mallone S et al. (2011). Saharan dust and associations between particulate matter and daily mortality in Rome, Italy. *Environmental Health Perspectives*, 119(10):1409–1414.
- Mann JK et al. (2010). Short-term effects of air pollution on wheeze in asthmatic children in Fresno, California. *Environmental Health Perspectives*, 118(10):1497–1502.
- Mar TF et al. (2005). Exhaled nitric oxide in children with asthma and short-term PM_{2.5} exposure in Seattle. *Environmental Health Perspectives*, 113(12):1791–1794.
- Mar TF et al. (2006). PM source apportionment and health effects. 3. Investigation of inter-method variations in associations between estimated source contributions of PM_{2.5} and daily mortality in Phoenix, AZ. *Journal of Exposure Science & Environmental Epidemiology*, 16(4):311–320.
- Marks GB et al. (2010). Respiratory health effects of exposure to low-NO_x unflued gas heaters in the classroom: a double-blind, cluster-randomized, crossover study. *Environmental Health Perspectives*, 118(10):1476–1482.

- Martínez-Canabal A et al. (2008). Effect of growth hormone on cyclooxygenase-2 expression in the hippocampus of rats chronically exposed to ozone. *International Journal of Neuroscience*, 118(3):455–469.
- Matalon S et al. (2009). Modification of surfactant protein D by reactive oxygen-nitrogen intermediates is accompanied by loss of aggregating activity, in vitro and in vivo. *FASEB Journal*, 23(5):1415–1430.
- Mauad T et al. (2008). Chronic exposure to ambient levels of urban particles affects mouse lung development. *American Journal of Respiratory and Critical Care Medicine*, 178(7):721–728.
- Mauderly JL et al. (2011). Health effects of subchronic inhalation exposure to simulated downwind coal combustion emissions. *Inhalation Toxicology*, 23(6):349–362.
- Mautz WJ et al. (1988). Effects of exercise exposure on toxic interactions between inhaled oxidant and aldehyde air pollutants. *Journal of Toxicology and Environmental Health*, 25(2):165–177.
- Mautz WJ et al. (2001). Respiratory tract responses to repeated inhalation of an oxidant and acid gas-particle air pollutant mixture. *Toxicological Sciences*, 61(2):331–341.
- McClellan RO, Hesterberg TW, Wall JC (2012). Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology. *Regulatory Toxicology and Pharmacology*, 63(2):225–258.
- McClellan RO et al. (2009). Critical considerations in evaluating scientific evidence of health effects of ambient ozone: a conference report. *Inhalation Toxicology*, 21(Suppl. 2):1–36.
- McConnell R et al. (2002). Asthma in exercising children exposed to ozone: a cohort study. *Lancet*, 359(9304):386–391.
- McConnell R et al. (2003). Prospective study of air pollution and bronchitic symptoms in children with asthma. *American Journal of Respiratory and Critical Care Medicine*, 168(7):790–797.
- McConnell R et al. (2006a). Traffic, susceptibility, and childhood asthma. *Environmental Health Perspectives*, 114(5):766–772.
- McConnell R et al. (2006b). Predicting residential ozone deficits from nearby traffic. *Science of the Total Environment*, 363(1-3):166–174.
- McConnell R et al. (2010). Childhood incident asthma and traffic-related air pollution at home and school. *Environmental Health Perspectives*, 118(7):1021–1026.

- McCreanor J et al. (2007). Respiratory effects of exposure to diesel traffic in persons with asthma. *New England Journal of Medicine*, 357(23):2348–2358.
- McDonald JD et al. (2012). *Part I. Biologic responses in rats and mice to subchronic inhalation of diesel exhaust from U.S. 2007-compliant engines: report on 1-, 3-, and 12-month exposures in the ACES bioassay*. Boston, Health Effects Institute (Research Report 166; <http://pubs.healtheffects.org/getfile.php?u=709>, accessed 17 March 2013):9–120.
- McDonnell WF, Stewart PW, Smith MV (2007). The temporal dynamics of ozone-induced FEV1 changes in humans: an exposure–response model. *Inhalation Toxicology*, 19(6–7):483–494.
- McDonnell WF, Stewart PW, Smith MV (2010). Prediction of ozone-induced lung function responses in humans. *Inhalation Toxicology*, 22(2):160–168.
- McDonnell WF et al. (2012). Prediction of lung function response for populations exposed to a wide range of ozone conditions. *Inhalation Toxicology*, 24(10):619–633.
- McGwin G, Lienert J, Kennedy JI (2010). Formaldehyde exposure and asthma in children: a systematic review. *Environmental Health Perspectives*, 118(3):313–317.
- McWhinney RD et al. (2011). Evaluation of the effects of ozone oxidation on redox-cycling activity of two-stroke engine exhaust particles. *Environmental Science & Technology*, 45(6):2131–2136.
- Medina S, Le Tertre A, Saklad M (2009). The Apehis project: Air Pollution and Health – a European Information System. *Air Quality, Atmosphere & Health*, 2(4):185–198.
- Meister K, Johansson C, Forsberg B (2012). Estimated short-term effects of coarse particles on daily mortality in Stockholm, Sweden. *Environmental Health Perspectives*, 120(3):431–436.
- Melén E et al. (2008). Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. *Environmental Health Perspectives*, 116(8):1077–1084.
- Mena-Carrasco M et al. (2012). Estimating the health benefits from natural gas use in transport and heating in Santiago, Chile. *Science of the Total Environment*, 429:257–265.
- Meng QY et al. (2012). Associations between personal exposures and ambient concentrations of nitrogen dioxide: a quantitative research synthesis. *Atmospheric Environment*, 57:322–329.

- Meng Z, Liu Y (2007). Cell morphological ultrastructural changes in various organs from mice exposed by inhalation to sulfur dioxide. *Inhalation Toxicology*, 19(6-7):543–551.
- Menichini E, Merli F (2012). Dibenzopyrenes, other PAHs with molecular weight 302, and selected carcinogenic PAHs seldom determined: identification and one-year quantification in urban air. *International Journal of Environmental Analytical Chemistry*, 92(14):1609–1625.
- Mercer RR, Costa DL, Crapo JD (1995). Effects of prolonged exposure to low doses of nitric oxide or nitrogen dioxide on the alveolar septa of the adult rat lung. *Laboratory Investigation*, 73(1):20–28.
- Meyer-Baron M, Schaeper M, Seeber A (2002). A meta-analysis for neurobehavioural results due to occupational mercury exposure. *Archives of Toxicology*, 76(3):127–136.
- Middleton N et al. (2008). A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. *Environmental Health*, 7:39.
- Miller FJ et al. (1980). Extrapulmonary effects of NO₂ as reflected by pentobarbital-induced sleeping time in mice. *Toxicology Letters*, 6(4-5):267–274.
- Miller FJ et al. (1987). Evaluating the toxicity of urban patterns of oxidant gases. II. Effects in mice from chronic exposure to nitrogen dioxide. *Journal of Toxicology and Environmental Health*, 21(1–2):99–112.
- Miller KA et al. (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. *New England Journal of Medicine*, 356(5):447–458.
- Miller LA et al. (2009). Ozone and allergen exposure during postnatal development alters the frequency and airway distribution of CD25+ cells in infant rhesus monkeys. *Toxicology and Applied Pharmacology*, 236(1):39–48.
- Mills NL et al. (2005). Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation*, 112(25):3930–3936.
- Mills NL et al. (2007). Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *New England Journal of Medicine*, 357(11):1075–1082.
- Mills NL et al. (2008). Exposure to concentrated ambient particles does not affect vascular function in patients with coronary heart disease. *Environmental Health Perspectives*, 116(6):709–715.

- Mills NL et al. (2011). Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. *European Heart Journal*, 32(21):2660–2671.
- Millstein J et al. (2004). Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children’s Health Study. *Archives of Environmental Health*, 59(10):505–514.
- Min JY et al. (2008). Lag effect of particulate air pollution on lung function in children. *Pediatric Pulmonology*, 43(5):476–480.
- Minelli C et al. (2011). Interactive effects of antioxidant genes and air pollution on respiratory function and airway disease: a HuGE review. *American Journal of Epidemiology*, 173(6):603–620.
- Miracolo MA et al. (2010). Photo-oxidation of low-volatility organics found in motor vehicle emissions: production and chemical evolution of organic aerosol mass. *Environmental Science & Technology*, 44(5):1638–1643.
- Mohsenin V (1987). Airway responses to nitrogen dioxide in asthmatic subjects. *Journal of Toxicology and Environmental Health*, 22(4):371–380.
- Mokoena ML et al. (2010). Ozone modulates the effects of imipramine on immobility in the forced swim test, and nonspecific parameters of hippocampal oxidative stress in the rat. *Metabolic Brain Disease*, 25(2):125–133.
- Mølhave L et al. (2005). Interaction between ozone and airborne particulate matter in office air. *Indoor Air*, 15(6):383–392.
- Monge-Corella S et al. (2008). Lung cancer mortality in towns near paper, pulp and board industries in Spain: a point source pollution study. *BMC Public Health*, 8:288.
- Monn C (2001). Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. *Atmospheric Environment*, 35(1):1–32.
- Moon JS et al. (2009). Respiratory health effects among schoolchildren and their relationship to air pollutants in Korea. *International Journal of Environmental Health Research*, 19(1):31–48.
- Morgan G et al. (2010). Effects of bushfire smoke on daily mortality and hospital admissions in Sydney, Australia. *Epidemiology*, 21(1):47–55.
- Morgenstern RD et al. (2012). *Accountability analysis of Title IV Phase 2 of the 1990 Clean Air Act Amendments*. Boston, Health Effects Institute (Research Report 168; <http://pubs.healtheffects.org/getfile.php?u=883>, accessed 17 March 2013).

- Morgenstern V et al. (2007). Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occupational and Environmental Medicine*, 64(1):8–16.
- Morgenstern V et al. (2008). Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *American Journal of Respiratory and Critical Care Medicine*, 177(12):1331–1337.
- Morio LA et al. (2001). Tissue injury following inhalation of fine particulate matter and hydrogen peroxide is associated with altered production of inflammatory mediators and antioxidants by alveolar macrophages. *Toxicology and Applied Pharmacology*, 177(3):188–199.
- Moshhammer H et al. (2006). Low levels of air pollution induce changes of lung function in a panel of schoolchildren. *European Respiratory Journal*, 27(6):1138–1143.
- Mostofsky E et al. (2012). Modeling the association between particle constituents of air pollution and health outcomes. *American Journal of Epidemiology*, 176(4):317–326.
- Mudway IS, Kelly FJ (2004). An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *American Journal of Respiratory and Critical Care Medicine*, 169(10):1089–1095.
- Naeher LP et al. (2007). Woodsmoke health effects: a review. *Inhalation Toxicology*, 19(1):67–106.
- Naess Ø et al. (2007). Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *American Journal of Epidemiology*, 165(4):435–443.
- NAS (2001). *Arsenic in drinking water: 2001 update*. Washington, DC, National Academy Press (<http://www.nap.edu/openbook.php?isbn=0309076293>, accessed 8 February 2013).
- Nawrot T et al. (2010). Occupational cadmium exposure and calcium excretion, bone density, and osteoporosis in men. *Journal of Bone and Mineral Research*, 25(6):1441–1445.
- Nickmilder M et al. (2007). Increase of exhaled nitric oxide in children exposed to low levels of ambient ozone. *Journal of Toxicology and Environmental Health, Part A*, 70(3–4):270–274.
- Nicolai T et al. (2003). Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *European Respiratory Journal*, 21(6):956–963.

- Nicolas M, Ramalho O, Maupetit F (2007). Reactions between ozone and building products: impact on primary and secondary emissions. *Atmospheric Environment*, 41(15):3129–3138.
- Nie A, Meng Z (2007). Sulfur dioxide derivatives modulate Na/Ca exchange currents and cytosolic $[Ca^{2+}]_i$ in rat myocytes. *Biochemical and Biophysical Research Communications*, 358(3):879–884.
- Noonan CW et al. (2011). *Assessing the impact of a wood stove replacement program on air quality and children's health*. Boston, Health Effects Institute (Research Report 162; <http://pubs.healtheffects.org/getfile.php?u=677>, accessed 17 March 2013):3–37; critique: 39–47.
- NTP (2012). *NTP monograph on health effects of low-level lead*. Research Triangle Park, NC, National Toxicology Program (<http://ntp.niehs.nih.gov/?objectid=4F04B8EA-B187-9EF2-9F9413C68E76458E>, accessed 22 March 2013).
- Nyberg F et al. (2000). Urban air pollution and lung cancer in Stockholm. *Epidemiology*, 11(5):487–495.
- Oakes M et al. (2012). Iron solubility related to particle sulfur content in source emission and ambient fine particles. *Environmental Science & Technology*, 46(12):6637–6644.
- O'Connor GT et al. (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. *Journal of Allergy and Clinical Immunology*, 121(5):1133–1139.e1.
- Oeder S et al. (2012). Toxicity and elemental composition of particulate matter from outdoor and indoor air of elementary schools in Munich, Germany. *Indoor Air*, 22(2):148–158.
- Oftedal B et al. (2008). Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology*, 19(1):129–137.
- Olsson D, Ekström M, Forsberg B (2012). Temporal variation in air pollution concentrations and preterm birth – a population based epidemiological study. *International Journal of Environmental Research and Public Health*, 9(1):272–285.
- Olsson D, Mogren I, Forsberg B (2013). Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. *BMJ Open*, 3(2).
- Orazio F et al. (2009). Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. *Environmental Health Perspectives*, 117(11):1780–1785.

- Ostro B, Rauch S, Green S (2011). Quantifying the health impacts of future changes in temperature in California. *Environmental Research*, 111(8):1258–1264.
- Ostro B et al. (2006). Fine particulate air pollution and mortality in nine California counties: results from CALFINE. *Environmental Health Perspectives*, 114(1):29–33.
- Ostro B et al. (2009). The effects of fine particle components on respiratory hospital admissions in children. *Environmental Health Perspectives*, 117(3):475–480.
- Ostro B et al. (2010). Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. *Environmental Health Perspectives*, 118(3):363–369.
- Ostro B et al. (2011). The effects of particulate matter sources on daily mortality: a case-crossover study of Barcelona, Spain. *Environmental Health Perspectives*, 119(12):1781–1787.
- Palli D et al. (2008). DNA adducts and PM(10) exposure in traffic-exposed workers and urban residents from the EPIC-Florence City study. *Science of the Total Environment*, 403(1-3):105–112.
- Pan G et al. (2010). Air pollution and children’s respiratory symptoms in six cities of Northern China. *Respiratory Medicine*, 104(12):1903–1911.
- Panesar NS (2008). Downsides to the nitrate-nitrite-nitric oxide pathway in physiology and therapeutics? *Nature Reviews Drug Discovery*, 7(8):710; author reply: 710.
- Papapostolou V et al. (2011). Laboratory evaluation of a prototype photochemical chamber designed to investigate the health effects of fresh and aged vehicular exhaust emissions. *Inhalation Toxicology*, 23(8):495–505.
- Park AK, Hong YC, Kim H (2011). Effect of changes in season and temperature on mortality associated with air pollution in Seoul, Korea. *Journal of Epidemiology and Community Health*, 65(4):368–375.
- Parker JD, Mendola P, Woodruff TJ (2008). Preterm birth after the Utah Valley Steel Mill closure: a natural experiment. *Epidemiology*, 19(6):820–823.
- Parker JD et al. (2011). The International Collaboration on Air Pollution and Pregnancy Outcomes: initial results. *Environmental Health Perspectives*, 119(7):1023–1028.
- Pasanen K et al. (2012). Mortality among population with exposure to industrial air pollution containing nickel and other toxic metals. *Journal of Occupational and Environmental Medicine*, 54(5):583–591.

- Pathmanathan S et al. (2003). Repeated daily exposure to 2 ppm nitrogen dioxide upregulates the expression of IL-5, IL-10, IL-13, and ICAM-1 in the bronchial epithelium of healthy human airways. *Occupational and Environmental Medicine*, 60(11):892–896.
- Pattenden S et al. (2010). Ozone, heat and mortality: acute effects in 15 British conurbations. *Occupational and Environmental Medicine*, 67(10):699–707.
- Peachey CJ et al. (2009). Deposition and solubility of airborne metals to four plant species grown at varying distances from two heavily trafficked roads in London. *Environmental Pollution*, 157(8–9):2291–2299.
- Peacock JL et al. (2011). Outdoor air pollution and respiratory health in patients with COPD. *Thorax*, 66(7):591–596.
- Pearson RL, Wachtel H, Ebi KL (2000). Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. *Journal of the Air & Waste Management Association*, 50(2):175–180.
- Pedersen M et al. (2009). Increased micronuclei and bulky DNA adducts in cord blood after maternal exposures to traffic-related air pollution. *Environmental Research*, 109(8):1012–1020.
- Peel JL et al. (2010). *Impact of improved air quality during the 1996 Summer Olympic Games in Atlanta on multiple cardiovascular and respiratory outcomes*. Boston, Health Effects Institute (Research Report 148; <http://pubs.healtheffects.org/getfile.php?u=564>, accessed 17 March 2013):3–23; discussion: 25–33.
- Peng RD et al. (2008). Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. *Journal of the American Medical Association*, 299(18):2172–2179.
- Penttinen P, Tiittanen P, Pekkanen J (2004). Mortality and air pollution in metropolitan Helsinki, 1988–1996. *Scandinavian Journal of Work, Environment & Health*, 30(Suppl. 2):19–27.
- Penttinen P et al. (2006). Source-specific fine particles in urban air and respiratory function among adult asthmatics. *Inhalation Toxicology*, 18(3):191–198.
- Perepu RSP et al. (2010). Enhanced death signaling in ozone-exposed ischemic-reperfused hearts. *Molecular and Cellular Biochemistry*, 336(1–2):55–64.
- Perera FP et al. (2011). Polycyclic aromatic hydrocarbons–aromatic DNA adducts in cord blood and behavior scores in New York City children. *Environmental Health Perspectives*, 119(8):1176–1181.

- Perera FP et al. (2012). Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6–7 years. *Environmental Health Perspectives*, 120(6):921–926.
- Perez L et al. (2009a). Size fractionate particulate matter, vehicle traffic, and case-specific daily mortality in Barcelona, Spain. *Environmental Science & Technology*, 43(13):4707–4714.
- Perez L et al. (2009b). Global goods movement and the local burden of childhood asthma in Southern California. *American Journal of Public Health*, 99(Suppl. 3):S622–S628.
- Perez L et al. (2012). Near-roadway pollution and childhood asthma: implications for developing ‘win-win’ compact urban development and clean vehicle strategies. *Environmental Health Perspectives*, 120(11):1619–1626.
- Pérez-Ballesta P et al. (2006). Population exposure to benzene: one day cross-sections in six European cities. *Atmospheric Environment*, 40(18):3355–3366.
- Peters A (2012). Epidemiology: air pollution and mortality from diabetes mellitus. *Nature Reviews Endocrinology*, 8(12):706–707.
- Peters A, Ruckerl R, Cyrus J (2011). Lessons from air pollution epidemiology for studies of engineered nanomaterials. *Journal of Occupational and Environmental Medicine*, 53(6 Suppl.):S8–S13.
- Peters A et al. (2006). Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Particle and Fibre Toxicology*, 3:13.
- Peters A et al. (2009). *The influence of improved air quality on mortality risks in Erfurt, Germany*. Boston, Health Effects Institute (Research Report 137; <http://pubs.healtheffects.org/getfile.php?u=437>, accessed 17 March 2013).
- Peters J et al. (1996). Effects of an ambient air pollution intervention and environmental tobacco smoke on children’s respiratory health in Hong Kong. *International Journal of Epidemiology*, 25(4):821–828.
- Petrick LM, Svidovsky A, Dubowski Y (2011). Thirdhand smoke: heterogeneous oxidation of nicotine and secondary aerosol formation in the indoor environment. *Environmental Science & Technology*, 45(1):328–333.
- Phalen RF, Mendez LB, Oldham MJ (2010). New developments in aerosol dosimetry. *Inhalation Toxicology*, 22(Suppl. 2):6–14.
- Plopper CG et al. (2007). Asthma/allergic airways disease: does postnatal exposure to environmental toxicants promote airway pathobiology? *Toxicologic Pathology*, 35(1):97–110.

- Polymenakou PN et al. (2008). Particle size distribution of airborne microorganisms and pathogens during an intense African dust event in the eastern Mediterranean. *Environmental Health Perspectives*, 116(3):292–296.
- Pope CA 3rd (1989). Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *American Journal of Public Health*, 79(5):623–628.
- Pope CA 3rd (1996). Particulate pollution and health: a review of the Utah Valley experience. *Journal of Exposure Analysis and Environmental Epidemiology*, 6(1):23–34.
- Pope CA 3rd (2012). Does reducing air pollution improve human health? Evidence from accountability studies. *EM Magazine*:16–21.
- Pope CA 3rd, Dockery DW (2006). Health effects of fine particulate air pollution: lines that connect. *Journal of the Air & Waste Management Association*, 56(6):709–742.
- Pope CA 3rd, Ezzati M, Dockery DW (2009). Fine-particulate air pollution and life expectancy in the United States. *New England Journal of Medicine*, 360(4):376–386.
- Pope CA 3rd, Rodermund DL, Gee MM (2007). Mortality effects of a copper smelter strike and reduced ambient sulfate particulate matter air pollution. *Environmental Health Perspectives*, 115(5):679–683.
- Pope CA 3rd et al. (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *American Journal of Respiratory and Critical Care Medicine*, 151(3 Pt 1):669–674.
- Pope CA 3rd et al. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Journal of the American Medical Association*, 287(9):1132–1141.
- Pope CA 3rd et al. (2004). Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*, 109(1):71–77.
- Pope CA 3rd et al. (2011). Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure–response relationships. *Environmental Health Perspectives*, 119(11):1616–1621.
- Popovicheva OB et al. (2011). Quantification of the hygroscopic effect of soot aging in the atmosphere: laboratory simulations. *Journal of Physical Chemistry A*, 115(3):298–306.

- Postlethwait EM, Bidani A (1989). Pulmonary disposition of inhaled NO₂-nitrogen in isolated rat lungs. *Toxicology and Applied Pharmacology*, 98(2):303–312.
- Powell H, Lee D, Bowman A (2012). Estimating constrained concentration–response functions between air pollution and health. *Environmetrics*, 23(3):228–237.
- Proietti E et al. (2013). Air pollution during pregnancy and neonatal outcome: a review. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 26(1):9–23.
- Puett RC et al. (2009). Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses’ Health Study. *Environmental Health Perspectives*, 117(11):1697–1701.
- Puett RC et al. (2011). Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. *Environmental Health Perspectives*, 119(8):1130–1135.
- Putaud JP et al. (2010). A European aerosol phenomenology. 3: Physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. *Atmospheric Environment*, 44(10):1308–1320.
- Qian Z et al. (2007). Short-term effects of gaseous pollutants on cause-specific mortality in Wuhan, China. *Journal of the Air & Waste Management Association*, 57(7):785–793.
- Qian Z et al. (2010). Seasonal pattern of the acute mortality effects of air pollution. *Journal of the Air & Waste Management Association*, 60(4):481–488.
- Qin G, Meng Z (2006a). The expressions of protooncogenes and CYP1A in lungs of rats exposed to sulfur dioxide and benzo(a)pyrene. *Regulatory Toxicology and Pharmacology*, 45(1):36–43.
- Qin G, Meng Z (2006b). Effect of sulfur dioxide inhalation on CYP2B1/2 and CYP2E1 in rat liver and lung. *Inhalation Toxicology*, 18(8):581–588.
- Qin G, Meng Z (2009). Effects of sulfur dioxide derivatives on expression of oncogenes and tumor suppressor genes in human bronchial epithelial cells. *Food and Chemical Toxicology*, 47(4):734–744.
- Qiu H et al. (2012). Effects of coarse particulate matter on emergency hospital admissions for respiratory diseases: a time-series analysis in Hong Kong. *Environmental Health Perspectives*, 120(4):572–576.
- Quan C et al. (2010). Comparative effects of inhaled diesel exhaust and ambient fine particles on inflammation, atherosclerosis, and vascular dysfunction. *Inhalation Toxicology*, 22(9):738–753.

- Que LG et al. (2011). Pulmonary function, bronchial reactivity, and epithelial permeability are response phenotypes to ozone and develop differentially in healthy humans. *Journal of Applied Physiology*, 111(3):679–687.
- Querol X et al. (2007). Source origin of trace elements in PM from regional background, urban and industrial sites of Spain. *Atmospheric Environment*, 41(34):7219–7231.
- Querol X et al. (2012). Variability of levels and composition of PM10 and PM2.5 in the Barcelona metro system. *Atmospheric Chemistry and Physics*, 12(11):5055–5076.
- Raaschou-Nielsen O et al. (2013). Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. *Diabetologia*, 56(1):36–46.
- Rabczenko D et al. (2005). [Short-term effect of air pollution with sulphur dioxide, black smoke and nitrogen dioxide on mortality of urban Polish population.] *Przegląd Epidemiologiczny*, 59(4):969–979 (in Polish).
- Rabinovitch N et al. (2004). Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. *Journal of Allergy and Clinical Immunology*, 114(5):1131–1137.
- Rage E et al. (2009). Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults. *Allergy*, 64(1):40–46.
- Rager JE et al. (2011). A toxicogenomic comparison of primary and photochemically altered air pollutant mixtures. *Environmental Health Perspectives*, 119(11):1583–1589.
- Rainham DGC, Smoyer-Tomic KE (2003). The role of air pollution in the relationship between a heat stress index and human mortality in Toronto. *Environmental Research*, 93(1):9–19.
- Rajagopalan S, Brook RD (2012). Air pollution and type 2 diabetes: mechanistic insights. *Diabetes*, 61(12):3037–3045.
- Rajaratnam U et al. (2011). Part 2. Time-series study on air pollution and mortality in Delhi. In: *Public health and air pollution in Asia (PAPA): coordinated studies of short-term exposure to air pollution and daily mortality in two Indian cities*. Boston, Health Effects Institute (Research Report 157; <http://pubs.healtheffects.org/getfile.php?u=623>, accessed 17 March 2013):61–108.
- Ranft U et al. (2009). Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environmental Research*, 109(8):1004–1011.
- Ranguelova K et al. (2012). Formation of reactive sulfite-derived free radicals by the activation of human neutrophils: an ESR study. *Free Radical Biology & Medicine*, 52(8):1264–1271.

- Ranzi A et al. (2004). Air pollution and respiratory status in asthmatic children: hints for a locally based preventive strategy. AIRE study. *European Journal of Epidemiology*, 19(6):567–576.
- Rappold AG et al. (2011). Peat bog wildfire smoke exposure in rural North Carolina is associated with cardiopulmonary emergency department visits assessed through syndromic surveillance. *Environmental Health Perspectives*, 119(10):1415–1420.
- Ravindra K, Sokhi R, Van Grieken R (2008). Atmospheric polycyclic aromatic hydrocarbons: source attribution, emission factors and regulation. *Atmospheric Environment*, 42(13):2895–2921.
- Reche C et al. (2011). New considerations for PM, Black Carbon and particle number concentration for air quality monitoring across different European cities. *Atmospheric Chemistry and Physics*, 11(13):6207–6227.
- Reiss R et al. (2007). Evidence of health impacts of sulfate- and nitrate-containing particles in ambient air. *Inhalation Toxicology*, 19(5):419–449.
- Ren C et al. (2008a). Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data. *Occupational and Environmental Medicine*, 65(4):255–260.
- Ren C et al. (2008b). Does temperature modify short-term effects of ozone on total mortality in 60 large eastern US communities? An assessment using the NMMAPS data. *Environment International*, 34(4):451–458.
- Ren C et al. (2011). Urinary 8-hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage induced by ambient pollution in the Normative Aging Study. *Occupational and Environmental Medicine*, 68(8):562–569.
- Ren YJ et al. (2008). [A case-crossover study on air pollutants and the mortality of stroke.] *Zhonghua Liu Xing Bing Xue Za Zhi*, 29(9):878–881 (in Chinese).
- Reponen T et al. (2003). Concentration gradient patterns of aerosol particles near interstate highways in the Greater Cincinnati airshed. *Journal of Environmental Monitoring*, 5(4):557–562.
- Rich DQ et al. (2012a). Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *Journal of the American Medical Association*, 307(19):2068–2078.
- Rich DQ et al. (2012b). Are ambient ultrafine, accumulation mode, and fine particles associated with adverse cardiac responses in patients undergoing cardiac rehabilitation? *Environmental Health Perspectives*, 120(8):1162–1169.

- Riediker M et al. (2003). Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. *Environmental Science & Technology*, 37(10):2084–2093.
- Riedl MA et al. (2012). *Allergic inflammation in the human lower respiratory tract affected by exposure to diesel exhaust*. Boston, Health Effects Institute (Research Report 165; <http://pubs.healtheffects.org/getfile.php?u=693>, accessed 17 March 2013):5–43; discussion:45–64.
- Rignell-Hydbom A et al. (2009). Exposure to cadmium and persistent organochlorine pollutants and its association with bone mineral density and markers of bone metabolism on postmenopausal women. *Environmental Research*, 109(8):991–996.
- Rijnders E et al. (2001). Personal and outdoor nitrogen dioxide concentrations in relation to degree of urbanization and traffic density. *Environmental Health Perspectives*, 109(Suppl. 3):411–417.
- Risher J (2003). *Elemental mercury and inorganic mercury compounds: human health aspects*. Geneva, World Health Organization (Concise International Chemical Assessment Document 50; <http://www.who.int/ipcs/publications/cicad/en/cicad50.pdf>, accessed 6 April 2013).
- Ritz B, Wilhelm M (2008). Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. *Basic & Clinical Pharmacology & Toxicology*, 102(2):182–190.
- Rivas-Arancibia S et al. (2000). Effects of taurine on ozone-induced memory deficits and lipid peroxidation levels in brains of young, mature, and old rats. *Environmental Research*, 82(1):7–17.
- Rivas-Arancibia S et al. (2010). Oxidative stress caused by ozone exposure induces loss of brain repair in the hippocampus of adult rats. *Toxicological Sciences*, 113(1):187–197.
- Roberts S, Martin M (2005). A critical assessment of shrinkage-based regression approaches for estimating the adverse health effects of multiple air pollutants. *Atmospheric Environment*, 39(33):6223–6230.
- Robinson AL et al. (2007). Rethinking organic aerosols: semivolatile emissions and photochemical aging. *Science*, 315(5816):1259–1262.
- Robison TW et al. (1993). Depression of stimulated arachidonate metabolism and superoxide production in rat alveolar macrophages following in vivo exposure to 0.5 ppm NO₂. *Journal of Toxicology and Environmental Health*, 38(3):273–292.

- Roemer WH, Van Wijnen JH (2001). Daily mortality and air pollution along busy streets in Amsterdam, 1987–1998. *Epidemiology*, 12(6):649–653.
- Roger LJ et al. (1990). Pulmonary function, airway responsiveness, and respiratory symptoms in asthmatics following exercise in NO₂. *Toxicology and Industrial Health*, 6(1):155–171.
- Rojas-Martinez R et al. (2007). Lung function growth in children with long-term exposure to air pollutants in Mexico City. *American Journal of Respiratory and Critical Care Medicine*, 176(4):377–384.
- Rombout PJ et al. (1986). Influence of exposure regimen on nitrogen dioxide-induced morphological changes in the rat lung. *Environmental Research*, 41(2):466–480.
- Romieu I et al. (1998). Evaluation of indoor ozone concentration and predictors of indoor-outdoor ratio in Mexico City. *Journal of the Air & Waste Management Association*, 48(4):327–335.
- Roorda-Knape MC et al. (1998). Air pollution from traffic in city districts near major motorways. *Atmospheric Environment*, 32(11):1921–1930.
- Rosenlund M et al. (2006). Long-term exposure to urban air pollution and myocardial infarction. *Epidemiology*, 17(4):383–390.
- Rosenlund M et al. (2009a). Traffic-related air pollution in relation to respiratory symptoms, allergic sensitisation and lung function in schoolchildren. *Thorax*, 64(7):573–580.
- Rosenlund M et al. (2009b). Traffic-generated air pollution and myocardial infarction. *Epidemiology*, 20(2):265–271.
- Routledge HC et al. (2006). Effect of inhaled sulphur dioxide and carbon particles on heart rate variability and markers of inflammation and coagulation in human subjects. *Heart*, 92(2):220–227.
- Royal Society (2008). *Ground-level ozone in the 21st century: future trends, impacts and policy implications*. London, Royal Society (<http://royalsociety.org/policy/publications/2008/ground-level-ozone/>, accessed 14 March 2013).
- Rubasinghe G et al. (2010). Simulated atmospheric processing of iron oxyhydroxide minerals at low pH: roles of particle size and acid anion in iron dissolution. *Proceedings of the National Academy of Sciences of the United States of America*, 107(15):6628–6633.

- Rubes J et al. (2005). Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. *Human Reproduction*, 20(10):2776–2783.
- Rückerl R et al. (2011). Health effects of particulate air pollution: a review of epidemiological evidence. *Inhalation Toxicology*, 23(10):555–592.
- Rudez G et al. (2009). Effects of ambient air pollution on hemostasis and inflammation. *Environmental Health Perspectives*, 117(6):995–1001.
- Rundell KW et al. (2007). Inhalation of ultrafine and fine particulate matter disrupts systemic vascular function. *Inhalation Toxicology*, 19(2):133–140.
- Ryan PH et al. (2005). Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *Journal of Allergy and Clinical Immunology*, 116(2):279–284.
- Sagai M, Ichinose T, Kubota K (1984). Studies on the biochemical effects of nitrogen dioxide. IV. Relation between the change of lipid peroxidation and the antioxidative protective system in rat lungs upon life span exposure to low levels of NO₂. *Toxicology and Applied Pharmacology*, 73(3):444–456.
- Sahsuvaroglu T et al. (2009). Spatial analysis of air pollution and childhood asthma in Hamilton, Canada: comparing exposure methods in sensitive subgroups. *Environmental Health*, 8:14.
- Salam MT, Islam T, Gilliland FD (2008). Recent evidence for adverse effects of residential proximity to traffic sources on asthma. *Current Opinion in Pulmonary Medicine*, 14(1):3–8.
- Samet JM et al. (2000). Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *New England Journal of Medicine*, 343(24):1742–1749.
- Samoli E et al. (2003). Investigating the dose–response relation between air pollution and total mortality in the APHEA-2 multicity project. *Occupational and Environmental Medicine*, 60(12):977–982.
- Samoli E et al. (2005). Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. *Environmental Health Perspectives*, 113(1):88–95.
- Samoli E et al. (2006). Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. *European Respiratory Journal*, 27(6):1129–1138.
- Samoli E et al. (2011a). Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environmental Research*, 111(3):418–424.

- Samoli E et al. (2011b). Does the presence of desert dust modify the effect of PM₁₀ on mortality in Athens, Greece? *Science of the Total Environment*, 409(11):2049–2054.
- Samoli E et al. (2013). Associations between fine and coarse particles and mortality in Mediterranean Cities: results from the MED-PARTICLES project. *Environmental Health Perspectives* (doi:10.1289/ehp.1206124; ehp.niehs.nih.gov/wp-content/uploads/121/5/ehp.1206124.pdf, accessed 17 May 2013).
- Sancini A et al. (2011). Exposure to urban stressors and free testosterone plasma values. *International Archives of Occupational and Environmental Health*, 84(6):609–616.
- Sarigiannis DA et al. (2011). Exposure to major volatile organic compounds and carbonyls in European indoor environments and associated health risk. *Environment International*, 37(4):743–765.
- Sarnat JA et al. (2001). Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? *Environmental Health Perspectives*, 109(10):1053–1061.
- Sarnat JA et al. (2007). Panel discussion review: session 1 – exposure assessment and related errors in air pollution epidemiologic studies. *Journal of Exposure Science & Environmental Epidemiology*, 17(Suppl. 2):S75–S82.
- Sarnat JA et al. (2008). Fine particle sources and cardiorespiratory morbidity: an application of chemical mass balance and factor analytical source-apportionment methods. *Environmental Health Perspectives*, 116(4):459–466.
- Sarnat SE et al. (2012). Air pollution and acute respiratory response in a panel of asthmatic children along the U.S. –Mexico border. *Environmental Health Perspectives*, 120(3):437–444.
- Sauerzapf V, Jones AP, Cross J (2009). Environmental factors and hospitalisation for chronic obstructive pulmonary disease in a rural county of England. *Journal of Epidemiology and Community Health*, 63(4):324–328.
- Saul RL, Archer MC (1983). Nitrate formation in rats exposed to nitrogen dioxide. *Toxicology and Applied Pharmacology*, 67(2):284–291.
- Savitz DA, Feingold L (1989). Association of childhood cancer with residential traffic density. *Scandinavian Journal of Work, Environment & Health*, 15(5):360–363.
- Scaife A et al. (2012). Lack of effect of nitrogen dioxide exposure on heart rate variability in patients with stable coronary heart disease and impaired left ventricular systolic function. *Occupational and Environmental Medicine*, 69(8):587–591.

- SCENIHR (2008). *The safety of dental amalgam and alternative dental restoration materials for patients and users*. Brussels, European Commission (http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_016.pdf, accessed 6 April 2013).
- Schauer JJ et al. (2006). *Characterization of metals emitted from motor vehicles*. Boston, Health Effects Institute (Research Report 133; <http://pubs.healtheffects.org/getfile.php?u=251>, accessed 17 March 2013):1–76; discussion: 77–88.
- Schelegle ES et al. (2009). 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. *American Journal of Respiratory and Critical Care Medicine*, 180(3):265–272.
- Schelegle ES et al. (2012). Modelling of individual subject ozone exposure response kinetics. *Inhalation Toxicology*, 24(7):401–415.
- Schikowski T et al. (2007). Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality? *Respiratory Research*, 8:20.
- Schildcrout JS et al. (2006). Ambient air pollution and asthma exacerbations in children: an eight-city analysis. *American Journal of Epidemiology*, 164(6):505–517.
- Schindler C et al. (2009). Improvements in PM10 exposure and reduced rates of respiratory symptoms in a cohort of Swiss adults (SAPALDIA). *American Journal of Respiratory and Critical Care Medicine*, 179(7):579–587.
- Schlesinger RB, Cassee F (2003). Atmospheric secondary inorganic particulate matter: the toxicological perspective as a basis for health effects risk assessment. *Inhalation Toxicology*, 15(3):197–235.
- Schneider A et al. (2010). Changes in deceleration capacity of heart rate and heart rate variability induced by ambient air pollution in individuals with coronary artery disease. *Particle and Fibre Toxicology*, 7:29.
- Schnelle-Kreis J et al. (1999). The effect of wind direction on the observed size distribution of particle adsorbed polycyclic aromatic hydrocarbons on an inner city sampling site. *Journal of Environmental Monitoring*, 1(4):357–360.
- Schreuder AB et al. (2006). Ambient woodsmoke and associated respiratory emergency department visits in Spokane, Washington. *International Journal of Occupational and Environmental Health*, 12(2):147–153.
- Schultz ES et al. (2012). Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. *American Journal of Respiratory and Critical Care Medicine*, 186(12):1286–1291.

- Schutte R et al. (2008). Bone resorption and environmental exposure to cadmium in women: a population study. *Environmental Health Perspectives*, 116(6):777–783.
- Schwartz J, Laden F, Zanobetti A (2002). The concentration–response relation between PM(2.5) and daily deaths. *Environmental Health Perspectives*, 110(10):1025–1029.
- Schwartz J et al. (2008). The effect of dose and timing of dose on the association between airborne particles and survival. *Environmental Health Perspectives*, 116(1):64–69.
- Schweizer C et al. (2007). Indoor time-microenvironment-activity patterns in seven regions of Europe. *Journal of Exposure Science & Environmental Epidemiology*, 17(2):170–181.
- Seaton A et al. (2005). The London Underground: dust and hazards to health. *Occupational and Environmental Medicine*, 62(6):355–362.
- Seilkop SK, Oller AR (2003). Respiratory cancer risks associated with low-level nickel exposure: an integrated assessment based on animal, epidemiological, and mechanistic data. *Regulatory Toxicology and Pharmacology*, 37(2):173–190.
- Seilkop SK et al. (2012). Identification of chemical components of combustion emissions that affect pro-atherosclerotic vascular responses in mice. *Inhalation Toxicology*, 24(5):270–287.
- Sekine K et al. (2004). Long term effects of exposure to automobile exhaust on the pulmonary function of female adults in Tokyo, Japan. *Occupational and Environmental Medicine*, 61(4):350–357.
- Serinelli M et al. (2010). [Acute effects of air pollution in Brindisi (Italy): a case-crossover analysis.] *Epidemiologia e Prevenzione*, 34(3):100–107 (in Italian).
- Shah PS, Balkhair T (2011). Air pollution and birth outcomes: a systematic review. *Environment International*, 37(2):498–516.
- Sharkhuu T et al. (2011). Effect of maternal exposure to ozone on reproductive outcome and immune, inflammatory, and allergic responses in the offspring. *Journal of Immunotoxicology*, 8(2):183–194.
- Sherwin RP, Richters V (1982). Hyperplasia of Type 2 pneumocytes following 0.34 ppm nitrogen dioxide exposure: quantitation by image analysis. *Archives of Environmental Health*, 37(5):306–315.
- Sherwin RP, Richters V (1995a). Effects of 0.25 ppm nitrogen dioxide on the developing mouse lung. Part 1. Quantitation of type 2 cells and measurements of alveolar walls. *Inhalation Toxicology*, 7(8):1173–1182.

- Sherwin RP, Richters V (1995b). Effects of 0.25 ppm nitrogen dioxide on the developing mouse lung. Part 2. Quantitation of elastic tissue and alveolar walls. *Inhalation Toxicology*, 7(8):1183–1194.
- Shima M (2007). Air pollution and serum C-reactive protein concentration in children. *Journal of Epidemiology*, 17(5):169–176.
- Shindell D et al. (2012). Simultaneously mitigating near-term climate change and improving human health and food security. *Science*, 335(6065):183–189.
- Shiraiwa M, Selzle K, Pöschl U (2012). Hazardous components and health effects of atmospheric aerosol particles: reactive oxygen species, soot, polycyclic aromatic compounds and allergenic proteins. *Free Radical Research*, 46(8):927–939.
- Sienra-Monge JJ et al. (2004). Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone. *Clinical and Experimental Immunology*, 138(2):317–322.
- Signorelli S et al. (2011). Nitrogen dioxide solubility and permeation in lipid membranes. *Archives of Biochemistry and Biophysics*, 512(2):190–196.
- Simpson R et al. (2005a). The short-term effects of air pollution on daily mortality in four Australian cities. *Australian and New Zealand Journal of Public Health*, 29(3):205–212.
- Simpson R et al. (2005b). The short-term effects of air pollution on hospital admissions in four Australian cities. *Australian and New Zealand Journal of Public Health*, 29(3):213–221.
- Sleiman M et al. (2010). Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential *thirdhand smoke* hazards. *Proceedings of the National Academy of Sciences of the United States of America*, 107(15):6576–6581.
- Smith AH et al. (2009). Increased lung cancer risks are similar whether arsenic is ingested or inhaled. *Journal of Exposure Science & Environmental Epidemiology*, 19(4):343–348.
- Smith KR et al. (2009). Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. *Lancet*, 374(9707):2091–2103.
- Smith RL, Xu B, Switzer P (2009). Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. *Inhalation Toxicology*, 21(Suppl. 2):37–61.

- Smith RL et al. (2000). Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. *Journal of the Air & Waste Management Association*, 50(8):1367–1379.
- Soares SRC et al. (2009). Air pollution and antibodies against modified lipoproteins are associated with atherosclerosis and vascular remodeling in hyperlipemic mice. *Atherosclerosis*, 207(2):368–373.
- Sokol RZ et al. (2006). Exposure to environmental ozone alters semen quality. *Environmental Health Perspectives*, 114(3):360–365.
- Son JY, Cho YS, Lee JT (2008). Effects of air pollution on postneonatal infant mortality among firstborn infants in Seoul, Korea: case-crossover and time-series analyses. *Archives of Environmental & Occupational Health*, 63(3):108–113.
- Son JY et al. (2012). Characterization of fine particulate matter and associations between particulate chemical constituents and mortality in Seoul, Korea. *Environmental Health Perspectives*, 120(6):872–878.
- Sørensen M et al. (2012). Long-term exposure to traffic-related air pollution associated with blood pressure and self-reported hypertension in a Danish cohort. *Environmental Health Perspectives*, 120(3):418–424.
- Sousa R et al. (2012). In vitro exposure of *Acer negundo* pollen to atmospheric levels of SO₂ and NO₂: effects on allergenicity and germination. *Environmental Science & Technology*, 46(4):2406–2412.
- Stafoggia M et al. (2008). Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. *American Journal of Epidemiology*, 167(12):1476–1485.
- Stafoggia M et al. (2010). Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. *American Journal of Respiratory and Critical Care Medicine*, 182(3):376–384.
- Stafoggia M et al. (2013). Short-term association between fine and coarse particulate matter and hospitalizations in Southern Europe – results from the MED-PARTICLES project. *Environmental Health Perspectives*, DOI:10.1289/ehp.1206151.
- Stanek LW et al. (2011a). Air pollution toxicology – a brief review of the role of the science in shaping the current understanding of air pollution health risks. *Toxicological Sciences*, 120(Suppl. 1):S8–S27.
- Stanek LW et al. (2011b). Attributing health effects to apportioned components and sources of particulate matter: an evaluation of collective results. *Atmospheric Environment*, 45(32):5655–5663.

- Steenberg PA et al. (2003). Adjuvant activity of various diesel exhaust and ambient particles in two allergic models. *Journal of Toxicology and Environmental Health, Part A*, 66(15):1421–1439.
- Steenberg PA et al. (2006). Relation between sources of particulate air pollution and biological effect parameters in samples from four European cities: an exploratory study. *Inhalation Toxicology*, 18(5):333–346.
- Steinvil A et al. (2008). Short-term exposure to air pollution and inflammation-sensitive biomarkers. *Environmental Research*, 106(1):51–61.
- Stenfors N et al. (2010). Ozone exposure enhances mast-cell inflammation in asthmatic airways despite inhaled corticosteroid therapy. *Inhalation Toxicology*, 22(2):133–139.
- Stieb DM, Judek S, Burnett RT (2002). Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. *Journal of the Air & Waste Management Association*, 52(4):470–484.
- Stieb DM, Judek S, Burnett RT (2003). Meta-analysis of time-series studies of air pollution and mortality: update in relation to the use of generalized additive models. *Journal of the Air & Waste Management Association*, 53(3):258–261.
- Stieb DM et al. (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environmental Health*, 8:25.
- Stone V et al. (2003). Investigating the potential for interaction between the components of PM(10). *Environmental Health and Preventive Medicine*, 7(6):246–253.
- Strak M et al. (2012). Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential – the RAPTES Project. *Environmental Health Perspectives*, 120(8):1183–1189.
- Strand V et al. (1996). Immediate and delayed effects of nitrogen dioxide exposure at an ambient level on bronchial responsiveness to histamine in subjects with asthma. *European Respiratory Journal*, 9(4):733–740.
- Stylianou M, Nicolich MJ (2009). Cumulative effects and threshold levels in air pollution mortality: data analysis of nine large US cities using the NMMAPS dataset. *Environmental Pollution*, 157(8–9):2216–2223.
- Suarez L et al. (2007). Maternal exposures to hazardous waste sites and industrial facilities and risk of neural tube defects in offspring. *Annals of Epidemiology*, 17(10):772–777.

- Sugiri D et al. (2006). The influence of large-scale airborne particle decline and traffic-related exposure on children's lung function. *Environmental Health Perspectives*, 114(2):282–288.
- Sugiura H, Ichinose M (2011). Nitrate stress in inflammatory lung diseases. *Nitric Oxide: Biology and Chemistry*, 25(2):138–144.
- Suh HH et al. (2011). Chemical properties of air pollutants and cause-specific hospital admissions among the elderly in Atlanta, Georgia. *Environmental Health Perspectives*, 119(10):1421–1428.
- Sun Q et al. (2005). Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *Journal of the American Medical Association*, 294(23):3003–3010.
- Sun Q et al. (2008). Ambient air particulate matter exposure and tissue factor expression in atherosclerosis. *Inhalation Toxicology*, 20(2):127–137.
- Sunil VR et al. (2007). Pulmonary effects of inhaled limonene ozone reaction products in elderly rats. *Toxicology and Applied Pharmacology*, 222(2):211–220.
- Surmeli NB et al. (2010). Peroxynitrite mediates active site tyrosine nitration in manganese superoxide dismutase. Evidence of a role for the carbonate radical anion. *Journal of the American Chemical Society*, 132(48):17174–17185.
- Sutton MA et al, eds (2011). *European nitrogen assessment – sources, effects and policy perspectives*. Cambridge, Cambridge University Press.
- Svartengren M et al. (2000). Short-term exposure to air pollution in a road tunnel enhances the asthmatic response to allergen. *European Respiratory Journal*, 15(4):716–724.
- Svendsen ER et al. (2007). Circulating neutrophil CD14 expression and the inverse association of ambient particulate matter on lung function in asthmatic children. *Annals of Allergy, Asthma & Immunology*, 99(3):244–253.
- Swanson KJ, Madden MC, Ghio AJ (2007). Biodiesel exhaust: the need for health effects research. *Environmental Health Perspectives*, 115(4):496–499.
- Swiston JR et al. (2008). Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. *European Respiratory Journal*, 32(1):129–138.
- Szyszkowicz M (2008). Ambient air pollution and daily emergency department visits for asthma in Edmonton, Canada. *International Journal of Occupational Medicine and Environmental Health*, 21(1):25–30.

- Tabacova S, Nikiforov B, Balabaeva L (1985). Postnatal effects of maternal exposure to nitrogen dioxide. *Neurobehavioral Toxicology and Teratology*, 7(6):785–789.
- Takano H et al. (2004). Nitrogen dioxide air pollution near ambient levels is an atherogenic risk primarily in obese subjects: a brief communication. *Experimental Biology and Medicine*, 229(4):361–364.
- Tam WWS et al. (2012). Effect of dust storm events on daily emergency admissions for respiratory diseases. *Respirology*, 17(1):143–148.
- Tamás G et al. (2006). Influence of ozone-limonene reactions on perceived air quality. *Indoor Air*, 16(3):168–178.
- Tank J et al. (2011). Effect of acute ozone induced airway inflammation on human sympathetic nerve traffic: a randomized, placebo controlled, crossover study. *PLoS ONE*, 6(4):e18737; doi:10.1371/journal.pone.0018737.
- Tankersley CG et al. (2010). Variation in echocardiographic and cardiac hemodynamic effects of PM and ozone inhalation exposure in strains related to *Nppa* and *Npr1* gene knock-out mice. *Inhalation Toxicology*, 22(8):695–707.
- Tashakkor AY, Chow KS, Carlsten C (2011). Modification by antioxidant supplementation of changes in human lung function associated with air pollutant exposure: a systematic review. *BMC Public Health*, 11:532.
- Taylor-Clark TE, Udem BJ (2010). Ozone activates airway nerves via the selective stimulation of TRPA1 ion channels. *Journal of Physiology (London)*, 588(Pt 3):423–433.
- Thach TQ et al. (2010). Air pollutants and health outcomes: Assessment of confounding by influenza. *Atmospheric Environment*, 44(11):1437–1442.
- Thaller EI et al. (2008). Moderate increases in ambient PM_{2.5} and ozone are associated with lung function decreases in beach lifeguards. *Journal of Occupational and Environmental Medicine*, 50(2):202–211.
- Thomas LDK et al. (2011). Dietary cadmium exposure and fracture incidence among men: a population-based prospective cohort study. *Journal of Bone and Mineral Research*, 26(7):1601–1608.
- Thompson AMS et al. (2010). Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. *Environmental Health Perspectives*, 118(1):120–124.
- Thorpe A, Harrison RM (2008). Sources and properties of non-exhaust particulate matter from road traffic: a review. *Science of the Total Environment*, 400(1–3):270–282.

- Tiitta P et al. (2002). Measurements and modelling of PM_{2.5} concentrations near a major road in Kuopio, Finland. *Atmospheric Environment*, 36(25):4057–4068.
- Tiittanen P et al. (1999). Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. *European Respiratory Journal*, 13(2):266–273.
- Tobías A et al. (2011). Short-term effects of particulate matter on total mortality during Saharan dust outbreaks: a case-crossover analysis in Madrid (Spain). *Science of the Total Environment*, 412-413:386–389.
- Tomao E et al. (2009). Luteinizing hormone (LH) levels in male workers exposed to urban stressors. *Science of the Total Environment*, 407(16):4591–4595.
- Tomei G et al. (2008). Exposure to urban stressor and effects on free testosterone in female workers. *Science of the Total Environment*, 392(2-3):198–202.
- Tomei G et al. (2009). Follicle-stimulating hormone levels in male workers exposed to urban chemical, physical, and psychosocial stressors. *Toxicology and Industrial Health*, 25(6):395–402.
- Tonne C et al. (2007). A case-control analysis of exposure to traffic and acute myocardial infarction. *Environmental Health Perspectives*, 115(1):53–57.
- Tonne C et al. (2008). Air pollution and mortality benefits of the London Congestion Charge: spatial and socioeconomic inequalities. *Occupational and Environmental Medicine*, 65(9):620–627.
- Tonne C et al. (2010). An approach for estimating the health effects of changes over time in air pollution: an illustration using cardio-respiratory hospital admissions in London. *Occupational and Environmental Medicine*, 67(6):422–427.
- TfL (2004). *Congestion charging central London: impacts monitoring – second annual report*. London, Transport for London
(<http://www.tfl.gov.uk/assets/downloads/Impacts-monitoring-report-2.pdf>, accessed 27 March 2013).
- TfL (2007). *Congestion charging central London: impacts monitoring – fifth annual report*. London, Transport for London.
- Trenga CA et al. (2006). Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest*, 129(6):1614–1622.
- Trijonis J (1979). Visibility in the Southwest – an exploration of the historical data base. *Atmospheric Environment*, 13(6):833–843.

- Trzcinka-Ochocka M et al. (2010). The effects of low environmental cadmium exposure on bone density. *Environmental Research*, 110(3):286–293.
- Tsai SS et al. (2003). Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. *Journal of Toxicology and Environmental Health, Part A*, 66(14):1341–1349.
- Tsai SS et al. (2006a). Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. *Inhalation Toxicology*, 18(8):549–554.
- Tsai SS et al. (2006b). Air pollution and postneonatal mortality in a tropical city: Kaohsiung, Taiwan. *Inhalation Toxicology*, 18(3):185–189.
- Tsujino I, Kawakami Y, Kaneko A (2005). Comparative simulation of gas transport in airway models of rat, dog, and human. *Inhalation Toxicology*, 17(9):475–485.
- Tsukue N et al. (2010). Acute effects of diesel emission from the urea selective catalytic reduction engine system on male rats. *Inhalation Toxicology*, 22(4):309–320.
- Tung KY, Tsai CH, Lee YL (2011). Microsomal epoxide hydroxylase genotypes/diplotypes, traffic air pollution, and childhood asthma. *Chest*, 139(4):839–848.
- Tunnicliffe WS, Burge PS, Ayres JG (1994). Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet*, 344(8939–8940):1733–1736.
- Tzivian L (2011). Outdoor air pollution and asthma in children. *Journal of Asthma*, 48(5):470–481.
- Ueda K, Nitta H, Odajima H (2010). The effects of weather, air pollutants, and Asian dust on hospitalization for asthma in Fukuoka. *Environmental Health and Preventive Medicine*, 15(6):350–357.
- Ueda K et al. (2012). Exposure to particulate matter and long-term risk of cardiovascular mortality in Japan: NIPPON DATA80. *Journal of Atherosclerosis and Thrombosis*, 19(3):246–254.
- UNEP, WMO (2011). *Integrated assessment of black carbon and tropospheric ozone: summary for decision makers*. Nairobi, United Nations Environment Programme (http://www.unep.org/dewa/Portals/67/pdf/BlackCarbon_SDM.pdf, accessed 26 March 2013).
- Ungvári I et al. (2012). Relationship between air pollution, *NFE2L2* gene polymorphisms and childhood asthma in a Hungarian population. *Journal of Community Genetics*, 3(1):25–33.

- Upadhyay S et al. (2008). Exposure to ultrafine carbon particles at levels below detectable pulmonary inflammation affects cardiovascular performance in spontaneously hypertensive rats. *Particle and Fibre Toxicology*, 5:19.
- Upmacis RK (2008). Atherosclerosis: a link between lipid intake and protein tyrosine nitration. *Lipid Insights*, (2):75.
- Urch B et al. (2005). Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environmental Health Perspectives*, 113(8):1052–1055.
- Vagaggini B et al. (1996). Effect of short-term NO₂ exposure on induced sputum in normal, asthmatic and COPD subjects. *European Respiratory Journal*, 9(9):1852–1857.
- Van den Hooven EH et al. (2011). Air pollution, blood pressure, and the risk of hypertensive complications during pregnancy: the generation R study. *Hypertension*, 57(3):406–412.
- Van den Hooven EH et al. (2012a). Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study. *Environmental Health Perspectives*, 120(1):150–156.
- Van den Hooven EH et al. (2012b). Air pollution exposure and markers of placental growth and function: the generation R study. *Environmental Health Perspectives*, 120(12):1753–1759.
- Van Erp A et al. (2012). Recent progress and challenges in assessing the effectiveness of air quality interventions towards improving public health: the HEI Experience. *EM Magazine*:22–28.
- Van Hee VC et al. (2009). Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. *American Journal of Respiratory and Critical Care Medicine*, 179(9):827–834.
- van Kempen E et al. (2012). Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary schoolchildren. *Environmental Research*, 115:18–25.
- Van Roosbroeck S et al. (2008). Validity of residential traffic intensity as an estimate of long-term personal exposure to traffic-related air pollution among adults. *Environmental Science & Technology*, 42(4):1337–1344.
- van Thriel C et al. (2010). Sensory and pulmonary effects of acute exposure to sulfur dioxide (SO₂). *Toxicology Letters*, 196(1):42–50.
- van Vliet P et al. (1997). Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environmental Research*, 74(2):122–132.

- van Winkle LS et al. (2010). Airway mast cells in a rhesus model of childhood allergic airways disease. *Toxicological Sciences*, 116(1):313–322.
- Veglia F et al. (2008). DNA adducts and cancer risk in prospective studies: a pooled analysis and a meta-analysis. *Carcinogenesis*, 29(5):932–936.
- Venn A et al. (2005). Proximity of the home to roads and the risk of wheeze in an Ethiopian population. *Occupational and Environmental Medicine*, 62(6):376–380.
- Verma V et al. (2009a). Physicochemical and toxicological profiles of particulate matter in Los Angeles during the October 2007 Southern California wildfires. *Environmental Science & Technology*, 43(3):954–960.
- Verma V et al. (2009b). Redox activity of urban quasi-ultrafine particles from primary and secondary sources. *Atmospheric Environment*, 43(40):6360–6368.
- Viana M et al. (2008). Inter-comparison of receptor models for PM source apportionment: case study in an industrial area. *Atmospheric Environment*, 42(16):3820–3832.
- Viel JF et al. (2008). Risk for non Hodgkin's lymphoma in the vicinity of French municipal solid waste incinerators. *Environmental Health*, 7:51.
- Vigotti MA, Serinelli M, Marchini L (2010). [Urban air pollution and children respiratory hospital admissions in Pisa (Italy): a time series and a case-crossover approach.] *Epidemiologia e Prevenzione*, 34(4):143–149 (in Italian).
- Villeneuve PJ et al. (2007). Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada. *Environmental Health*, 6:40.
- Viren JR, Silvers A (1994). Unit risk estimates for airborne arsenic exposure: an updated view based on recent data from two copper smelter cohorts. *Regulatory Toxicology and Pharmacology*, 20(2):125–138.
- von Klot S et al. (2005). Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. *Circulation*, 112(20):3073–3079.
- Vrijheid M et al. (2011). Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. *Environmental Health Perspectives*, 119(5):598–606.
- Vyskocil A, Viau C, Lamy S (1998). Peroxyacetyl nitrate: review of toxicity. *Human & Experimental Toxicology*, 17(4):212–220.

- Wagner U et al. (2006). Analysis of airway secretions in a model of sulfur dioxide induced chronic obstructive pulmonary disease (COPD). *Journal of Occupational Medicine and Toxicology*, 1:12.
- Waldner CL (2008). The association between exposure to the oil and gas industry and beef calf mortality in Western Canada. *Archives of Environmental & Occupational Health*, 63(4):220–240.
- Waldner CL (2009). Risk of abortion and stillbirth in cow-calf herds exposed to the oil and gas industry in Western Canada. *Archives of Environmental & Occupational Health*, 64(1):29–45.
- Waldner CL, Stryhn H (2008). Risk of nonpregnancy, risk of disposal for pregnant cows, and duration of the calving interval in cow-calf herds exposed to the oil and gas industry in Western Canada. *Archives of Environmental & Occupational Health*, 63(4):241–261.
- Waldner CL, Clark EG (2009). Association between exposure to emissions from the oil and gas industry and pathology of the immune, nervous, and respiratory systems, and skeletal and cardiac muscle in beef calves. *Archives of Environmental & Occupational Health*, 64(1):6–27.
- Wang S et al. (2010). Quantifying the air pollutants emission reduction during the 2008 Olympic Games in Beijing. *Environmental Science & Technology*, 44(7):2490–2496.
- Wang W et al. (2009). Atmospheric particulate matter pollution during the 2008 Beijing Olympics. *Environmental Science & Technology*, 43(14):5314–5320.
- Wang Y et al. (2012). Biomarkers of chromosomal damage in peripheral blood lymphocytes induced by polycyclic aromatic hydrocarbons: a meta-analysis. *International Archives of Occupational and Environmental Health*, 85(1):13–25.
- Wegesser TC, Last JA (2008). Lung response to coarse PM: bioassay in mice. *Toxicology and Applied Pharmacology*, 230(2):159–166.
- Wegesser TC, Pinkerton KE, Last JA (2009). California wildfires of 2008: coarse and fine particulate matter toxicity. *Environmental Health Perspectives*, 117(6):893–897.
- Weichenthal S (2012). Selected physiological effects of ultrafine particles in acute cardiovascular morbidity. *Environmental Research*, 115:26–36.
- Weichenthal S et al. (2011). Traffic-related air pollution and acute changes in heart rate variability and respiratory function in urban cyclists. *Environmental Health Perspectives*, 119(10):1373–1378.

- Weinmayr G et al. (2010). Short-term effects of PM10 and NO2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environmental Health Perspectives*, 118(4):449–457.
- Weisel CP et al. (2005). *Relationships of indoor, outdoor, and personal air (RIOPA). Part I. Collection methods and descriptive analyses*. Boston, Health Effects Institute (Research Report 130, Part 1; <http://pubs.healtheffects.org/getfile.php?u=25>, accessed 17 March 2013):1–107; discussion:109–127.
- Weitzberg E, Hezel M, Lundberg JO (2010). Nitrate-nitrite-nitric oxide pathway: implications for anesthesiology and intensive care. *Anesthesiology*, 113(6):1460–1475.
- Wenten M et al. (2009). Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: an example of epistasis in gene-environment interactions. *American Journal of Epidemiology*, 170(12):1494–1501.
- Weschler CJ (2006). Ozone's impact on public health: contributions from indoor exposures to ozone and products of ozone-initiated chemistry. *Environmental Health Perspectives*, 114(10):1489–1496.
- Weschler CJ (2011). Chemistry in indoor environments: 20 years of research. *Indoor Air*, 21(3):205–218.
- Weschler CJ et al. (2006). Workgroup report: indoor chemistry and health. *Environmental Health Perspectives*, 114(3):442–446.
- WHO (2003). *Elemental mercury and inorganic mercury compounds: human health aspects*. Geneva, World Health Organization (Concise International Chemical Assessment Document; <http://www.who.int/ipcs/publications/cicad/en/cicad50.pdf>, accessed 6 April 2013).
- WHO (2011). *Arsenic in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality*. Geneva, World Health Organization (http://www.who.int/water_sanitation_health/dwq/chemicals/arsenic.pdf, accessed 6 April 2013).
- WHO (2013). WHO regional offices [web site]. Geneva, World Health Organization (<http://www.who.int/about/regions/en/index.html>, accessed 9 March 2013).
- WHO Regional Office for Europe (2000). *Air quality guidelines for Europe*, 2nd edition (CD ROM version). Copenhagen, WHO Regional Office for Europe (<http://www.euro.who.int/en/what-we-do/health-topics/environment-and->

- health/air-quality/publications/pre2009/who-air-quality-guidelines-for-europe,-2nd-edition,-2000-cd-rom-version, accessed 30 March 2013).
- WHO Regional Office for Europe (2005). *Health effects of transport-related air pollution*. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0006/74715/E86650.pdf, accessed 30 March 2013).
- WHO Regional Office for Europe (2006). *Air quality guidelines global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide*. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf, accessed 6 April 2013).
- WHO Regional Office for Europe (2007). *Health risks of heavy metals from long-range transboundary air pollution*. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0007/78649/E91044.pdf, accessed 28 March 2013).
- WHO Regional Office for Europe (2010). *WHO guidelines for indoor air quality: selected pollutants*. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf, accessed 6 April 2013).
- WHO Regional Office for Europe, CLRTAP (2006). *Health risks of particulate matter from long-range transboundary air pollution*. Bonn, WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0006/78657/E88189.pdf, accessed 8 March 2013).
- Wichmann J et al. (2010). PM2.5, soot and NO2 indoor–outdoor relationships at homes, pre-schools and schools in Stockholm, Sweden. *Atmospheric Environment*, 44(36):4536–4544.
- Wilfong ER et al. (2011). The acute and long-term effects of Middle East sand particles on the rat airway following a single intratracheal instillation. *Journal of Toxicology and Environmental Health, Part A*, 74(20):1351–1365.
- Wilhelm M et al. (2008). Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. *Environmental Health Perspectives*, 116(9):1254–1260.
- Wilhelm M et al. (2012). Traffic-related air toxics and term low birth weight in Los Angeles County, California. *Environmental Health Perspectives*, 120(1):132–138.
- Willers SM et al. (2013). Fine and coarse particulate air pollution in relation to respiratory health in Sweden. *European Respiratory Journal* (doi: 10.1183/09031936.00088212;

- <http://erj.ersjournals.com/content/early/2013/01/10/09031936.00088212.abstract>, accessed 9 May 2013).
- Williams R et al. (2012). Impact of personal and ambient-level exposures to nitrogen dioxide and particulate matter on cardiovascular function. *International Journal of Environmental Health Research*, 22(1):71–91.
- Wisthaler A, Weschler CJ (2010). Reactions of ozone with human skin lipids: sources of carbonyls, dicarbonyls, and hydroxycarbonyls in indoor air. *Proceedings of the National Academy of Sciences of the United States of America*, 107(15):6568–6575.
- Witten A et al. (2005). Effects of nitrogen dioxide on allergic airway responses in subjects with asthma. *Journal of Occupational and Environmental Medicine*, 47(12):1250–1259.
- Wolkoff P et al. (2008). Acute airway effects of ozone-initiated d-limonene chemistry: importance of gaseous products. *Toxicology Letters*, 181(3):171–176.
- Wong CM et al. (2008). Public health and air pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environmental Health Perspectives*, 116(9):1195–1202.
- Wong CM et al. (2010a). Part 4. Interaction between air pollution and respiratory viruses: time-series study of daily mortality and hospital admissions in Hong Kong. In. *Public health and air pollution in Asia (PAPA): coordinated studies of short-term exposure to air pollution and daily mortality in four cities*. Boston, Health Effects Institute (Research Report 154, Part 4; <http://pubs.healtheffects.org/getfile.php?u=594>, accessed 17 March 2013):9–99.
- Wong CM et al. (2010b). *Part 5. Public health and air pollution in Asia (PAPA): a combined analysis of four studies of air pollution and mortality*. Boston, Health Effects Institute (Research Report 154; <http://pubs.healtheffects.org/getfile.php?u=595>, accessed 17 March 2013).
- Wong CM et al. (2012). *Impact of the 1990 Hong Kong legislation for restriction on sulfur content in fuel*. Boston, Health Effects Institute (Research Report 170; <http://pubs.healtheffects.org/getfile.php?u=744>, accessed 17 March 2013):5–102.
- Woodruff TJ, Darrow LA, Parker JD (2008). Air pollution and postneonatal infant mortality in the United States, 1999–2002. *Environmental Health Perspectives*, 116(1):110–115.
- Wu J et al. (2011). Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. *Environmental Research*, 111(5):685–692.

- Wu Q, Magnus JH, Hentz JG (2010). Urinary cadmium, osteopenia, and osteoporosis in the US population. *Osteoporosis International*, 21(8):1449–1454.
- Wu S et al. (2007). [Effect of ammonium sulfate aerosol on the photochemical reaction of toluene/ NO(x)/air mixture.] *Huan Jing Ke Xue*, 28(6):1183–1187 (in Chinese).
- Wu S et al. (2010). Association of heart rate variability in taxi drivers with marked changes in particulate air pollution in Beijing in 2008. *Environmental Health Perspectives*, 118(1):87–91.
- Xie J, Fan R, Meng Z (2007). Protein oxidation and DNA-protein crosslink induced by sulfur dioxide in lungs, livers, and hearts from mice. *Inhalation Toxicology*, 19(9):759–765.
- Yamazaki S et al. (2007). Intracerebral haemorrhage associated with hourly concentration of ambient particulate matter: case-crossover analysis. *Occupational and Environmental Medicine*, 64(1):17–24.
- Yamazaki S et al. (2011). Effect of hourly concentration of particulate matter on peak expiratory flow in hospitalized children: a panel study. *Environmental Health*, 10:15.
- Yang CY et al. (2004). Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. *Environment International*, 30(4):519–523.
- Yang CY et al. (2007). Air pollution and hospital admissions for asthma in a subtropical city: Taipei, Taiwan. *Journal of Toxicology and Environmental Health, Part A*, 70(2):111–117.
- Yang YF et al. (2009). Asthma drugs counter-regulate interleukin-8 release stimulated by sodium sulfite in an A549 cell line. *The Journal of Asthma*, 46(3):238–243.
- Yazar M, Bellander T, Merritt AS (2011). Personal exposure to carcinogenic and toxic air pollutants in Stockholm, Sweden: A comparison over time. *Atmospheric Environment*, 45(17):2999–3004.
- Yoon HK, Cho HY, Kleeberger SR (2007). Protective role of matrix metalloproteinase-9 in ozone-induced airway inflammation. *Environmental Health Perspectives*, 115(11):1557–1563.
- Yorifuji T et al. (2011). Diesel vehicle emission and death rates in Tokyo, Japan: a natural experiment. *Science of the Total Environment*, 409(19):3620–3627.
- Yue W et al. (2007). Ambient source-specific particles are associated with prolonged repolarization and increased levels of inflammation in male coronary artery disease patients. *Mutation Research*, 621(1-2):50–60.

- Zanobetti A, Schwartz J (2008). Temperature and mortality in nine US cities. *Epidemiology*, 19(4):563–570.
- Zanobetti A, Schwartz J (2009). The effect of fine and coarse particulate air pollution on mortality: a national analysis. *Environmental Health Perspectives*, 117(6):898–903.
- Zanobetti A, Schwartz J (2011). Ozone and survival in four cohorts with potentially predisposing diseases. *American Journal of Respiratory and Critical Care Medicine*, 184(7):836–841.
- Zanobetti A et al. (2009). Fine particulate air pollution and its components in association with cause-specific emergency admissions. *Environmental Health*, 8:58.
- Zanobetti A et al. (2010). Reduction in heart rate variability with traffic and air pollution in patients with coronary artery disease. *Environmental Health Perspectives*, 118(3):324–330.
- Zanobetti A et al. (2012). Summer temperature variability and long-term survival among elderly people with chronic disease. *Proceedings of the National Academy of Sciences of the United States of America*, 109(17):6608–6613.
- Zauli Sajani S et al. (2011). Saharan dust and daily mortality in Emilia-Romagna (Italy). *Occupational and Environmental Medicine*, 68(6):446–451.
- Zeka A, Schwartz J (2004). Estimating the independent effects of multiple pollutants in the presence of measurement error: an application of a measurement-error-resistant technique. *Environmental Health Perspectives*, 112(17):1686–1690.
- Zhang J et al. (2013). *Cardiorespiratory biomarker responses in healthy young adults to drastic air quality changes surrounding the 2008 Beijing Olympics*. Boston, Health Effects Institute (Research Report 174; <http://pubs.healtheffects.org/getfile.php?u=912>, accessed 17 March 2013).
- Zhang KM et al. (2005). Evolution of particle number distribution near roadways. Part III: Traffic analysis and on-road size resolved particulate emission factors. *Atmospheric Environment*, 39(22):4155–4166.
- Zhang Y et al. (2010). Dual role of vitamin C utilization in NO₂-induced oxidative stress in lung tissues of mice. *Bulletin of Environmental Contamination and Toxicology*, 84(6):662–666.
- Zhao H et al. (2008). Protective effects of salicylic acid and vitamin C on sulfur dioxide-induced lipid peroxidation in mice. *Inhalation Toxicology*, 20(9):865–871.

- Zhao Z et al. (2008). Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. *Environmental Health Perspectives*, 116(1):90–97.
- Zhou J et al. (2011). Time-series analysis of mortality effects of fine particulate matter components in Detroit and Seattle. *Environmental Health Perspectives*, 119(4):461–466.
- Zhou Y, Levy JI (2007). Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. *BMC Public Health*, 7:89.
- Zhou YM et al. (2003). Oxidative stress and NFκB activation in the lungs of rats: a synergistic interaction between soot and iron particles. *Toxicology and Applied Pharmacology*, 190(2):157–169.
- Zhu N et al. (2012). Environmental nitrogen dioxide (NO₂) exposure influences development and progression of ischemic stroke. *Toxicology Letters*, 214(2):120–130.
- Zhu Y et al. (2002). Study of ultrafine particles near a major highway with heavy-duty diesel traffic. *Atmospheric Environment*, 36(27):4323–4335.
- Zhu Y et al. (2006). Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. *Environmental Science & Technology*, 40(8):2531–2536.
- Zurbier M et al. (2010). Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. *Environmental Health Perspectives*, 118(6):783–789.
- Zurbier M et al. (2011a). Respiratory effects of commuters' exposure to air pollution in traffic. *Epidemiology*, 22(2):219–227.
- Zurbier M et al. (2011b). In-traffic air pollution exposure and CC16, blood coagulation, and inflammation markers in healthy adults. *Environmental Health Perspectives*, 119(10):1384–1389.

List of invited experts participating in REVIHAAP

Scientific Advisory Committee

This Committee supervises the implementation of the project on Review of evidence on health aspects of air pollution (REVIHAAP) and ensure the highest possible quality and relevance of its outputs. The following experts are the members of the Committee:

- Hugh Ross Anderson, United Kingdom
- Bert Brunekreef, The Netherlands
- Aaron Cohen, United States
- Klea Katsouyanni, Greece
- Daniel Krewski, Canada
- Wolfgang G. Kreyling, Germany
- Nino Künzli, Switzerland
- Xavier Querol, Spain

Expert authors

The following experts are involved in the review of the evidence on health aspects of air pollution to draft the evaluation of the evidence and answers to key questions on particulate matter, ground-level ozone and other air pollutants and their mixtures, and general questions, as part of the REVIHAAP project:

- Richard Atkinson, United Kingdom
- Lars Barregård, Sweden
- Tom Bellander, Sweden
- Rick Burnett, Canada
- Flemming Cassee, The Netherlands
- Eduardo de Oliveira Fernandes, Portugal
- Francesco Forastiere, Italy
- Bertil Forsberg, Sweden
- Susann Henschel, Ireland
- Gerard Hoek, The Netherlands
- Stephen T Holgate, United Kingdom
- Nicole Janssen, The Netherlands
- Matti Jantunen, Finland
- Frank Kelly, United Kingdom
- Timo Lanki, Finland
- Inga Mills, United Kingdom
- Ian Mudway, United Kingdom
- Mark Nieuwenhuijsen, Spain
- Bart Ostro, United States
- Annette Peters, Germany

- David Phillips, United Kingdom
- C. Arden Pope III, United States
- Regula Rapp, Switzerland
- Gerd Sällsten, Sweden
- Evi Samoli, Greece
- Peter Straehl, Switzerland
- Annemoon van Erp, United States
- Heather Walton, United Kingdom
- Martin Williams, United Kingdom

External reviewers

The following experts have provided comments on the technical content and clarity of the document, for various sections of the draft material:

- Joseph Antó, Spain
- Alena Bartonova, Norway
- Vanessa Beaulac, Canada
- Michael Brauer, Canada
- Hyunok Choi, United States
- Bruce Fowler, United States
- Sandro Fuzzi, Italy
- Krystal Godri, Canada
- Patrick Goodman, Ireland
- Dan Greenbaum, United States
- Jonathan Grigg, United Kingdom
- Otto Hänninen, Finland
- Roy Harrison, United Kingdom
- Peter Hoet, Belgium
- Barbara Hoffmann, Germany
- Phil Hopke, United States
- Fintan Hurley, United Kingdom
- Barry Jessiman, Canada
- Haidong Kan, China
- Michal Krzyzanowski, Germany
- Thomas Kuhlbusch, Germany
- Morton Lippmann, United States
- Robert Maynard, United Kingdom
- Sylvia Medina, France
- Lidia Morawska, Australia
- Antonio Mutti, Italy
- Tim Nawrot, Belgium
- Juha Pekkanen, Finland
- Mary Ross, United States

- Jürgen Schneider, Austria
- Joel Schwartz, United States
- Frances Silverman, Canada
- Jordi Sunyer, Spain

Observers at WHO Expert Group meetings

These individuals participated in at least one of the WHO meetings organized for project REVIHAAP, in the capacity of observer:

- Markus Amann, IIASA
- Arlean Rhode, CONCAWE
- Wolfgang Schoepp, IIASA
- André Zuber, European Commission

WHO Secretariat

The WHO European Centre for Environment and Health, Bonn, WHO Regional Office for Europe, coordinated the work and the development of this publication:

- Svetlana Cincurak
- Kelvin Fong
- Marie-Eve Héroux (project leader from September 2012)
- Michal Krzyzanowski (project leader up to August 2012)
- Elizabet Paunovic
- Helena Shkarubo