



**World Health  
Organization**

REGIONAL OFFICE FOR **Europe**

# Health risks of air pollution in Europe – HRAPIE project

Recommendations for  
concentration–response  
functions for cost–benefit  
analysis of particulate matter,  
ozone and nitrogen dioxide



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

## ABSTRACT

This document presents recommendations for concentration–response functions for key pollutants to be included in cost–benefit analysis supporting the revision of the European Union’s air quality policy. It provides a response to a question posed by the European Commission in the framework of the WHO “Health risks of air pollution in Europe – HRAPIE” project. The essential background to this response was developed through a review of evidence on health aspects of air pollutants summarized by an earlier WHO project, “Review of evidence on health aspects of air pollution – REVIHAAP”. This report recommends concentration–response functions and associated background information for several mortality and morbidity effects associated with short- and long-term exposure to particulate matter, ozone and nitrogen dioxide.

This publication arises from the HRAPIE project and was co-funded by the European Union.

### Keywords

AIR POLLUTANTS  
ENVIRONMENTAL HEALTH  
EVIDENCE-BASED PRACTICE  
GUIDELINES  
HEALTH POLICY  
NITROGEN DIOXIDE  
OZONE  
PARTICULATE MATTER

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

Publications  
WHO Regional Office for Europe  
UN City, Marmorvej 51  
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
1. Introduction.....	1
1.1. Cost–effectiveness and cost–benefit analyses of EU air quality policies .....	1
1.2. Development process for HRAPIE project recommendations .....	2
1.3. Implementation of the HRAPIE project recommendations.....	3
1.4. Possible double counting of effects of various pollutants.....	12
2. Long-term PM exposure.....	12
2.1. Effects of long-term PM <sub>2.5</sub> exposure on all-cause mortality.....	12
2.2. Effects of long-term PM <sub>2.5</sub> exposure on cause-specific mortality.....	15
2.3. Effects of long-term PM <sub>10</sub> exposure on postneonatal mortality.....	17
2.4. Effects of long-term PM <sub>10</sub> exposure on prevalence of bronchitis in children.....	17
2.5. Effects of long-term PM <sub>10</sub> exposure on incidence of chronic bronchitis in adults .....	18
3. Short-term PM exposure .....	19
3.1. Effects of short-term PM <sub>2.5</sub> exposure on all-cause mortality.....	19
3.2. Effects of short-term PM <sub>2.5</sub> exposure on hospital admissions for CVDs and respiratory diseases .....	21
3.3. Effects of short-term PM <sub>2.5</sub> exposure on RADs.....	22
3.4. Effects of short-term PM <sub>2.5</sub> exposure on work days lost .....	23
3.5. Effects of short-term PM <sub>10</sub> exposure on incidence of asthma symptoms in asthmatic children .....	24
4. Long-term O <sub>3</sub> exposure.....	24
4.1. Effects of long-term O <sub>3</sub> exposure on respiratory mortality.....	24
5. Short-term O <sub>3</sub> exposure .....	25
5.1. Effects of short-term O <sub>3</sub> exposure on all-cause mortality.....	25
5.2. Effects of short-term O <sub>3</sub> exposure on cardiovascular and respiratory mortality.....	26
5.3. Effects of short-term O <sub>3</sub> exposure on hospital admissions for CVDs and respiratory diseases.....	26
5.4. Effects of short-term O <sub>3</sub> exposure on MRADs.....	27
6. Long-term NO <sub>2</sub> exposure.....	28
6.1. Effects of long-term NO <sub>2</sub> exposure on all-cause mortality.....	28
6.2. Effects of long-term NO <sub>2</sub> exposure on bronchitic symptoms in asthmatic children .....	30
7. Short-term NO <sub>2</sub> exposure.....	32
7.1. Effects of short-term NO <sub>2</sub> exposure on all-cause mortality .....	32

7.2. Effects of short-term NO <sub>2</sub> exposure on hospital admissions for respiratory diseases	.33
References	.....34
Annex 1. Contributors to the HRAPIE project	.....42
Annex 2. Effects of long-term NO <sub>2</sub> exposure on asthma prevalence in children – qualitative description	.....44
Annex 3. Background information on estimation of effects of NO <sub>2</sub> on bronchitic symptoms in asthmatic children	.....47
Annex 4. Effects of black carbon exposure – qualitative description	.....54

## **Acknowledgements**

The “Health risks of air pollution in Europe – HRAPIE” project was co-funded by the WHO Regional Office for Europe and the European Commission under Contribution Agreement 07.0307/2012/626738/SUB/ENV.C3. The WHO European Centre for Environment and Health, Bonn, Germany, coordinated the project implementation and the development of this publication.

## Abbreviations

ACS	American Cancer Society
AHSMOG	Loma Linda University Adventist Health and Smog study
APED	air pollution epidemiology database
APHEA	Air Pollution and Health: a European Approach project
APHENA	Air Pollution and Health: a European and North American approach study
CAFE	Clean Air for Europe programme
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	concentration–response function
CVD	cardiovascular disease
EC	European Commission
ES	effect estimate
EU	European Union
EUROSTAT	statistical office of the European Union
GBD 2010	Global Burden of Disease 2010 study
HRAPIE	Health risks of air pollution in Europe project
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, ninth revision
ICD-10	International Classification of Diseases, tenth revision
IIASA	International Institute for Applied Systems Analysis
ISAAC	International Study on Asthma and Allergies in Childhood
MDB	European mortality database
MRAD	minor restricted activity day
NLCSAIR	Netherlands Cohort Study on Diet and Cancer, air quality investigation section
NO <sub>2</sub>	nitrogen dioxide
O <sub>3</sub>	ozone
OC	organic carbon
PATY	Pollution and the Young study
PM	particulate matter
PM <sub>10</sub>	particulate matter with an aerodynamic diameter smaller than 10 µm
PM <sub>2.5</sub>	particulate matter with an aerodynamic diameter smaller than 2.5 µm
ppb	parts per billion
RAD	restricted activity day
REVIHAAP	Review of evidence on health aspects of air pollution project
RR	relative risk
SAPALDIA	Swiss Study on Air Pollution and Lung Disease in Adults
SD	standard deviation
Σ	sum

## 1. Introduction

In the framework of the European Union (EU)’s declaration of 2013 as the Year of Air, the WHO Regional Office for Europe coordinated two international projects (“Review of evidence on health aspects of air pollution – REVIHAAP” and “Health risks of air pollution in Europe – HRAPIE”) to provide the European Commission (EC) and its stakeholders with evidence-based advice on the health aspects of air pollution. This advice is grounded on a review of the latest scientific evidence on the health effects of all pollutants regulated in EC directives 2008/50/EC and 2004/107/EC (EC, 2013), as well as additional air pollutants of relevance for health, conducted by a large group of invited experts from eminent institutions across the world (see Annex 1 for contributors to the HRAPIE project).

The results of these projects support the comprehensive revision of EU air quality policies taking place in 2013. To offer effective advice, the REVIHAAP and HRAPIE projects address a list of 26 key policy-relevant questions posed by the EC. The questions cover general aspects of importance for air quality management, as well as specific topics concerning health aspects of individual air pollutants.

As part of the HRAPIE project, experts were asked to formulate a response to question D5: “What concentration–response functions for key pollutants should be included in cost–benefit analysis supporting the revision of EU air quality policy?” The essential background to this response was developed through a review of evidence on health aspects of air pollutants summarized by the REVIHAAP project report (WHO, 2013a). In particular, answers to REVIHAAP project questions on the pollutants, health outcomes and concentration–response functions (CRFs) that could be recommended for health impact assessment (questions A6 for particulate matter (PM), B3 for ozone (O<sub>3</sub>) and C4 for nitrogen dioxide (NO<sub>2</sub>)) provided the basis for the selection of the CRFs recommended for inclusion in the policy analysis.

A separate part of the HRAPIE project documented new emerging risks to health from air pollution through a survey of experts. These survey results are available in a separate report (WHO, 2013b).

### 1.1. Cost–effectiveness and cost–benefit analyses of EU air quality policies

Responding to the EC’s request, the HRAPIE project specifically addressed both cost–effectiveness and cost–benefit analyses. Analysis of cost–effectiveness aims to identify the pollution reduction strategies that will most effectively deliver a given benefit (for example, reduction of mortality or of the number of disability-adjusted life-years lost due to exposure). The work supporting the EU’s Thematic Strategy on Air Pollution compared about 50 different strategy options, each requiring substantial modelling effort. For practical reasons, therefore, the number of CRFs recommended should be kept to a minimum (optimally, one per pollutant) facilitating selection of the policy options.

The cost–benefit analysis performed for the policy option(s) selected aims to compare the benefits of actions to reduce environmental burdens against their costs. This requires a complete assessment of all impacts: omission of some impacts causes underestimation of the

benefit of the pollution reduction, which might lead to incorrect conclusions. Therefore, the choice of CRFs selected for this analysis should be more comprehensive, including a complete set of all health outcomes linked to the exposure indicated by research evidence. Cost–benefit analysis should include options based on various alternative assumptions and may also test the extent to which the results might change if effects supported by weaker evidence were considered.

The health experts involved in the HRAPIE project were in favour of recommending several alternative options for analysis to reflect the uncertainties of risk assessment. This would require repetition of the cost–effectiveness analysis for each option and would thus multiply the number of results for consideration in policy selection. Such an approach would significantly complicate the policy debate for stakeholders and policy-makers, so only one methodology for cost–effectiveness analysis was selected: estimating the impacts of exposure to PM<sub>2.5</sub> (PM with an aerodynamic diameter smaller than 2.5 µm) and to O<sub>3</sub> on mortality. Morbidity effects were not included for two reasons: cost–benefit analyses show that mortality impacts dominate the analysis as a whole and mortality data are complete and better standardized in EU countries. Nevertheless, the HRAPIE experts recommended more options – including effects on mortality and morbidity – for further cost–benefit analysis, also covering the effects of exposure to NO<sub>2</sub>. Other sources – such as IIASA (2013) – offer more detailed information on the cost–effectiveness analysis of various policy options at the EU level.

## **1.2. Development process for HRAPIE project recommendations**

The discussion at the WHO REVIHAAP/HRAPIE expert meeting held in Bonn on 15–17 January 2013 provided general direction for further work on CRFs linking mortality with PM<sub>2.5</sub> and O<sub>3</sub> in cost–effectiveness analysis, as well as for the outcomes to be considered in the cost–benefit analysis. This was followed by intensive discussion between the members of the Scientific Advisory Committee and other experts using electronic media (e-mails and teleconferences), and provided input to the International Institute for Applied Systems Analysis (IIASA) cost–effectiveness analysis in March 2013 (IIASA, 2013). Work on health outcomes to be considered in the cost–benefit analysis continued and included effects of PM, O<sub>3</sub> and NO<sub>2</sub>.

Where available, recent meta-analyses of epidemiological studies were used as the main data for the HRAPIE project's conclusions. In some other cases, a dedicated meta-analysis was used in the scope of the HRAPIE project, taking information gathered by the air pollution epidemiology database (APED) of St. George's Hospital Medical School, University of London. This database contains details and results from time-series studies of mortality and hospital admissions indexed in Medline, Embase, and Web of Knowledge to May 2011 (Anderson et al., 2007). The United Kingdom Department of Health is currently funding a systematic review and meta-analyses of results from time-series studies of PM, O<sub>3</sub> and NO<sub>2</sub> using APED. That review also provided evidence for the HRAPIE project analysis.

The Scientific Advisory Committee meeting convened by the WHO European Centre for Environment and Health in Bonn, Germany, on 13 June 2013 reviewed the preliminary results of the experts' work. Invited external reviewers also provided detailed comments on a draft version of this report in August 2013. The experts used the meeting's recommendations

and external reviewers' comments to support their discussions in order to finalize their contributions.

### **1.3. Implementation of the HRAPIE project recommendations**

This document presents the HRAPIE project recommendations for input into the cost–benefit analysis of the selected policy options. The experts agreed that, according to the REVIHAAP project report (WHO, 2013a), there is sufficient evidence for the causality of effects for each of the CRFs recommended. They classified the pollutant–outcome pairs recommended for cost–benefit analysis into two categories:

- Group A: pollutant–outcome pairs for which enough data are available to enable reliable quantification of effects;
- Group B: pollutant–outcome pairs for which there is more uncertainty about the precision of the data used for quantification of effects.

The recommendations consider specific conditions in EU countries – particularly in relation to the range of PM, O<sub>3</sub> and NO<sub>2</sub> concentrations expected to be observed in the EU in 2020 – as well as the availability of baseline health data. As a result, generalization of the recommended approaches to other regions of the globe or individual countries, or to particular mixtures at the local level, may be not appropriate.

Table 1 provides an overview of the recommended elements of the cost–benefit analysis for the three pollutants. Recommendations for CRFs are given as relative risks (RRs). Some of the studies used to set these CRFs provided odds ratios, which approximate to RRs under certain assumptions, such as for small concentration increments and for rare events. The use of odds ratios may be more accurate for larger concentration increments, such as in burden calculations or if policy options are analysed by the difference in total effects with and without the policy (which involves using the total pollutant concentration in the interim calculations). Annexes 2 and 3 give examples of the method of calculation using odds ratios.

Europe-wide modelling for particles is only available for PM<sub>2.5</sub>, so in cases where CRFs are expressed against PM<sub>10</sub> (PM with an aerodynamic diameter smaller than 10 µm) in the literature, a conversion has to be employed in the cost–benefit analysis to assess the equivalent impact per unit of PM<sub>2.5</sub>. This is achieved by multiplying the CRF for PM<sub>10</sub> by a factor of 1.54, assuming that effects are attributable to the PM<sub>2.5</sub> fraction of PM<sub>10</sub>, based on an estimated 65% of PM<sub>10</sub> being in the PM<sub>2.5</sub> size range. This PM<sub>2.5</sub>/PM<sub>10</sub> ratio of 0.65 is considered an average for the European population; however, in specific locations the ratio may be in the range 0.4–0.8 and a local estimate would be preferable for the conversion.

Annexes 2 and 4 present additional options for estimating the effects of air pollution on health (such as the effects of long-term exposure to NO<sub>2</sub> on asthma and of black carbon on mortality and hospital admissions); the experts discussed these within the HRAPIE project but did not recommend them for current assessment of EU air quality policies.

Among the effect estimates (ESs) for pollutant–outcome pairs listed in Table 1 those marked with an asterisk (\*) contribute to the total effect (i.e. the effects are additive) of either the limited set (Group A\*) or the extended set (Group B\*) of effects. Calculation of the range of overall costs and benefits should be based on the following principles:

- the calculation of a limited set of impacts based on the sum ( $\Sigma$ ) of Group A\*;
- the range of uncertainty around the limited estimate, from  $\Sigma$  minimum (Group A\*, Group A) to  $\Sigma$  maximum (Group A\*, Group A), possibly combined with Monte Carlo estimates based on confidence intervals (CIs) of RRs – minimum/maximum functions select smaller/larger effect in the related alternative options;
- the calculation of an extended set of impacts based on  $\Sigma$  Group A\* +  $\Sigma$  Group B\*;
- the range of uncertainty around the extended estimate, from  $\Sigma$  [minimum (Group A\*, Group A) + minimum (Group B\*, Group B)] to  $\Sigma$  [maximum (Group A\*, Group A) + maximum (Group B\*, Group B)], possibly combined with Monte Carlo estimates based on CIs of RRs.

The CIs associated with the recommended CRFs quantify the random error and the variability attributed to heterogeneity in the epidemiologic ESs used for health impact assessment; this is a small part of the total uncertainty in the risk estimates produced by the health impact assessment and cost–benefit analysis processes. Other uncertainties are associated with other aspects of the overall process – for example, in the measurement and modelling of pollution, the estimates of background rates for morbidity (those for mortality are based on population-wide data) and monetary valuation. Some less tangible issues arise from the transferability to the EU as a whole of CRFs and background rates from locations where studies were carried out or data were otherwise gathered; from agreeing what particular pollutant–outcome pairs should be used together to estimate the health impacts of particular policies and measures; and from assessing the uncertainty of an overall estimate of effects, aggregated (after conversion to monetary values) over the various pollutant–outcome pairs of either Group A\* or Group B\* proposed here, or indeed any intermediate variant of these two sets.

An effort was made to give the best evidence-based estimate of the relationship between the pollutant and that health outcome for each pollutant–outcome pair included. To avoid double counting, the HRAPIE experts proposed explicit rules of adjustment or recommended the exclusion of some pollutant–outcome pairs whose effect might – at least to a substantial degree – already have been accounted for. Acute effects of air pollution can occur with a delay of a few days or even more. In selecting risk coefficients linking short-term exposures to health outcomes, however, the distributed lags were not taken into account, possibly resulting in underestimation of the overall effect. In addition, some health outcomes on which there is evidence of the effects of air pollution were excluded because of difficulties in attaching monetary values reliably – for example, low birth weight and lung function. Further, the use of Group A\* rather than Group B\* may lead to underestimation of risk, as there is sufficient evidence of a causal relationship for all pollutant–outcome pairs.

The details of the uncertainty assessment and other issues related to the implementation of the HRAPIE project’s recommendations in the cost–benefit analysis fall outside of the remit of the HRAPIE project. The report on implementation of the HRAPIE project’s recommendations for the European air pollution cost–benefit analysis (Holland, 2013) provides a thorough description of the methods.

Table 1. CRFs recommended by the HRAPIE project

<b>PM, long-term exposure</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
PM <sub>2.5</sub> , annual mean	Mortality, all-cause (natural), age 30+ years	A*	1.062 (1.040–1.083)	All	European mortality database (MDB) (WHO, 2013c), rates for deaths from all natural causes (International Classification of Diseases, tenth revision (ICD-10) chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	Meta-analysis of 13 cohort studies with results: Hoek et al. (2013)	
PM <sub>2.5</sub> , annual mean	Mortality, cerebrovascular disease (includes stroke), ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and trachea, bronchus and lung cancer, age 30+ years	A	Global Burden of Disease (GBD) 2010 study (IHME, 2013), supra-linear exponential decay saturation model (age-specific), linearized by the PM <sub>2.5</sub> expected in 2020 under the current legislation scenario	All	European detailed mortality database (WHO, 2013d), ICD-10 codes cerebrovascular: I60–I63, I65–I67, I69.0–I69.3; ischaemic heart disease: I20–I25; COPD: J40–J44, J47; trachea, bronchus and lung cancer: C33–C34, D02.1–D02.2, D38.1	CRFs used in the GBD 2010 study	An alternative to all-cause mortality  Both age-specific and all-age estimates to be calculated to assess the potential effect of age stratification
PM <sub>10</sub> , annual mean	Postneonatal (age 1–12 months) infant mortality, all-cause	B*	1.04 (1.02, 1.07)	All	European Health for All database (WHO, 2013e) and United Nations projections	Woodruff, Grillo and Schoendorf (1997), based on 4 million infants in the United States	More recent analysis (Woodruff, Darrow and Parker, 2008) based on 3.5 million infants in the United States gives RR = 1.18 (1.06, 1.31) for respiratory postneonatal infant mortality; the older analysis is recommended as a source of RR due to unavailability of cause-specific postneonatal mortality data

<b>PM, long-term exposure (continued)</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
PM <sub>10</sub> , annual mean	Prevalence of bronchitis in children, age 6–12 (or 6–18) years	B*	1.08 (0.98–1.19)	All	Mean prevalence from the Pollution and the Young (PATY) study: 18.6% (range 6–41%)	PATY study (Hoek et al., 2012) analysing data from about 40 000 children living in nine countries	Heterogeneity of the association (p<0.10) between studies
PM <sub>10</sub> , annual mean	Incidence of chronic bronchitis in adults (age 18+ years)	B*	1.117 (1.040–1.189)	All	Annual incidence 3.9 per 1000 adults based on the Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA)	Combination of results from longitudinal studies Loma Linda University Adventist Health and Smog (AHSMOG) and SAPALDIA	Two studies with different odds ratios/RRs; cost–benefit analysis based on symptoms reporting is weak indication of clinically recognized COPD

<b>PM, short-term exposure</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
PM <sub>2.5</sub> , daily mean	Mortality, all-cause, all ages	A	1.0123 (1.0045–1.0201)	All	MDB (WHO, 2013c)	APED meta-analysis of 12 single-city and one multicity studies	For information only: not proposed as an alternative to long-term PM <sub>2.5</sub> exposure  The premature deaths attributed to short-term changes of PM <sub>2.5</sub> are already accounted for in estimating the effects of long-term exposure
PM <sub>2.5</sub> , daily mean	Hospital admissions, cardiovascular diseases (CVDs) (includes stroke), all ages	A*	1.0091 (1.0017–1.0166)	All	European hospital morbidity database (WHO, 2013f), ICD, ninth revision (ICD-9) codes 390–459; ICD-10 codes I00–I99	APED meta-analysis of four single-city and one multicity studies	

<b>PM, short-term exposure (continued)</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
PM <sub>2.5</sub> , daily mean	Hospital admissions, respiratory diseases, all ages	A*	1.0190 (0.9982–1.0402)	All	European hospital morbidity database (WHO, 2013f), ICD-9 codes 460-519; ICD-10 codes J00–J99	APED meta-analysis of three single-city studies	
PM <sub>2.5</sub> , two-week average, converted to PM <sub>2.5</sub> , annual average	Restricted activity days (RADs), all ages	B**	1.047 (1.042–1.053)	All	19 RADs per person per year: baseline rate from the Ostro and Rothschild (1989) study	Study of 12 000 adults followed for six years in 49 metropolitan areas of the United States (Ostro, 1987)	One 1987 study from the United States; no data of background rate in Europe
PM <sub>2.5</sub> , two-week average, converted to PM <sub>2.5</sub> , annual average	Work days lost, working-age population (age 20–65 years)	B*	1.046 (1.039–1.053)	All	European Health for All database (WHO, 2013e)	Study of 12 000 adults followed for six years in 49 metropolitan areas of the United States (Ostro, 1987)	High variability of background rates based on reported sick absenteeism in Europe, reflecting intercountry differences in definition
PM <sub>10</sub> , daily mean	Incidence of asthma symptoms in asthmatic children aged 5–19 years	B*	1.028 (1.006–1.051)	All	Prevalence of asthma in children based on “severe asthma” in the International Study on Asthma and Allergies in Childhood (ISAAC) (Lai et al., 2009) – western Europe: 4.9%; northern and eastern Europe: 3.5%. Daily incidence of symptoms in this group: 17% (interpolation from several panel studies)	Meta-analysis of 36 panel studies of asthmatic children conducted in 51 populations, including 36 from Europe, (Weinmayr et al., 2010)	Varying definition of the target population and of the daily occurrence of symptoms

\*\* Only residual RADs to be added to total effect, after days in hospital, work days lost and days with symptoms are accounted for.

<b>O<sub>3</sub>, long-term exposure</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
O <sub>3</sub> , summer months (April–September), average of daily maximum 8-hour mean over 35 parts per billion (ppb)	Mortality, respiratory diseases, age 30+ years	B	1.014 (1.005–1.024)	>35 ppb (>70 µg/m <sup>3</sup> )	MDB (WHO, 2013c), ICD-10 codes J00–J99	Single-pollutant models from American Cancer Society (ACS) data analysis (Jerrett et al., 2009a)	Alternative to effects of short-term O <sub>3</sub> on all-cause mortality

<b>O<sub>3</sub>, short-term exposure</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
O <sub>3</sub> , daily maximum 8-hour mean	Mortality, all (natural) causes, all ages	A*	1.0029 (1.0014–1.0043)	>35 ppb (>70 µg/m <sup>3</sup> )	MDB (WHO, 2013c), ICD-10 chapters I–XVIII, codes A–R	Air Pollution and Health: a European and North American approach study (APHENA), based on data from 32 European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	APHENA study, based on full range of observed O <sub>3</sub> concentrations, including levels <35 ppb; thus effects at O <sub>3</sub> <35 ppb are ignored
O <sub>3</sub> , daily maximum 8-hour mean	Mortality, all (natural) causes, all ages	A	1.0029 (1.0014–1.0043)	>10 ppb (>20 µg/m <sup>3</sup> )	MDB (WHO, 2013c), ICD-10 chapters I–XVIII, codes A–R	APHENA study based on data from 32 European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	Alternative to the assessment for O <sub>3</sub> >35 ppb only
O <sub>3</sub> , daily maximum 8-hour mean	Mortality, CVDs and respiratory diseases, all ages	A	CVD: 1.0049 (1.0013–1.0085); respiratory: 1.0029 (0.9989–1.0070)	>35 ppb (>70 µg/m <sup>3</sup> )	MDB (WHO, 2013c), ICD-10 codes CVD: I00–I99; respiratory: J00–J99	APHENA study based on data from 32 European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	Alternative to all-cause mortality analysis
O <sub>3</sub> , daily maximum 8-hour mean	Mortality, CVDs and respiratory diseases, all ages	A	CVD: 1.0049 (1.0013–1.0085); respiratory: 1.0029 (0.9989–1.0070)	>10 ppb (>20 µg/m <sup>3</sup> )	MDB (WHO, 2013c), ICD-10 codes CVD: I00–I99; respiratory: J00–J99	APHENA study based on data from 32 European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	Alternative to the cause-specific assessment for O <sub>3</sub> >35 ppb only

<b>O<sub>3</sub>, short-term exposure (continued)</b>							
<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>	<b>Pollutant metric</b>
O <sub>3</sub> , daily maximum 8-hour mean	Hospital admissions, CVDs (excluding stroke) and respiratory diseases, age 65+ years	A*	CVD: 1.0089 (1.0050–1.0127); respiratory: 1.0044 (1.0007–1.0083)	>35 ppb (>70 µg/m <sup>3</sup> )	European hospital morbidity database (WHO, 2013f), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	APHENA study based on data from eight European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	APHENA study based on all range of observed O <sub>3</sub> concentrations, including levels <35 ppb; thus effects at O <sub>3</sub> <35 ppb are ignored
O <sub>3</sub> , daily maximum 8-hour mean	Hospital admissions, CVD (excluding stroke) and respiratory diseases, age 65+ years	A	CVD: 1.0089 (1.0050–1.0127); respiratory: 1.0044 (1.0007–1.0083)	>10 ppb (>20 µg/m <sup>3</sup> )	European hospital morbidity database (WHO, 2013f), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	APHENA study based on data from eight European cities; coefficients adjusted for PM <sub>10</sub> in two-pollutant model	Alternative to the assessment for O <sub>3</sub> >35 ppb only
O <sub>3</sub> , daily maximum 8-hour mean	Minor restricted activity days (MRADs), all ages	B*	1.0154 (1.0060–1.0249)	>35 ppb (>70 µg/m <sup>3</sup> )	7.8 days per year, based on Ostro and Rothchild (1989)	Ostro and Rothchild's (1989) six separate analyses of annual data 1976–1981 of the United States National Health Interview Survey	One study from the United States in 1989, used as a source of both RR and background rates
O <sub>3</sub> , daily maximum 8-hour mean	MRADs, all ages	B	1.0154 (1.0060–1.0249)	>10 ppb (>20 µg/m <sup>3</sup> )	7.8 days per year, based on Ostro and Rothchild (1989)	Ostro and Rothchild's (1989) six separate analyses of annual data 1976–1981 of the United States National Health Interview Survey	Alternative to the assessment for O <sub>3</sub> >35 ppb only

NO <sub>2</sub> , long-term exposure							
Pollutant metric	Health outcome	Group	RR (95% CI) per 10 µg/m <sup>3</sup>	Range of concentration	Source of background health data	Source of CRF	Comments
NO <sub>2</sub> , annual mean	Mortality, all (natural) causes, age 30+ years	B*	1.055 (1.031–1.080)	>20 µg/m <sup>3</sup>	MDB (WHO, 2013c), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 WHO Regional Office for Europe countries, latest available data	Meta-analysis of all (11) cohort studies published before January 2013 by Hoek et al. (2013); RR based on single-pollutant models	Some of the long-term NO <sub>2</sub> effects may overlap with effects from long-term PM <sub>2.5</sub> (up to 33%); this is therefore recommended for quantification under Group B to avoid double counting in Group A analysis
NO <sub>2</sub> , annual mean	Prevalence of bronchitic symptoms in asthmatic children aged 5–14 years	B*	1.021 (0.990–1.060) per 1 µg/m <sup>3</sup> change in annual mean NO <sub>2</sub>	All	Background rate of asthmatic children, “asthma ever”, in Lai et al. (2009) – western Europe: 15.8%, standard deviation (SD) 7.8%; northern and eastern Europe: 5.1%, SD 2.7%, with a recommended alternative of “severe wheeze” in Lai et al. (2009) – western Europe: 4.9%; northern and eastern Europe: 3.5%  Prevalence of bronchitic symptoms among asthmatic children 21.1% to 38.7% (Migliore et al., 2009; McConnell et al., 2003)	Southern California Children’s Health Study (McConnell et al., 2003); coefficient from two-pollutant model with organic carbon (OC) (coefficients from models with PM <sub>10</sub> or PM <sub>2.5</sub> are higher)	Based on only one available longitudinal study providing NO <sub>2</sub> coefficient adjusted for other pollutants  Supported by studies of long-term exposure to NO <sub>2</sub> and lung function and by the wider evidence on NO <sub>2</sub> and respiratory outcomes from other types of studies

<b>NO<sub>2</sub>, short-term exposure</b>							
<b>Pollutant metric</b>	<b>Health outcome</b>	<b>Group</b>	<b>RR (95% CI) per 10 µg/m<sup>3</sup></b>	<b>Range of concentration</b>	<b>Source of background health data</b>	<b>Source of CRF</b>	<b>Comments</b>
NO <sub>2</sub> , daily maximum 1-hour mean	Mortality, all (natural) causes, all ages	A*	1.0027 (1.0016–1.0038)	All	MDB (WHO, 2013c), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	Air Pollution and Health: a European Approach (APHEA)-2 project with data from 30 European cities; RR adjusted for PM <sub>10</sub>	
NO <sub>2</sub> , daily maximum 1-hour mean	Hospital admissions, respiratory diseases, all ages	A	1.0015 (0.9992–1.0038)	All	European hospital morbidity database (WHO, 2013f), ICD-9 codes 460–519; ICD-10 codes J00–J99	APED meta-analysis of four studies published before 2006; coefficient from single-pollutant model  WHO (2013a) noted that the estimates for this pollutant–outcome pair were robust to adjustment to co-pollutants	Alternative to the estimates based on 24-hour NO <sub>2</sub> average (preferred due to availability of more studies)
NO <sub>2</sub> , 24-hour mean	Hospital admissions, respiratory diseases, all ages	A*	1.0180 (1.0115–1.0245)	All	European hospital morbidity database (WHO, 2013f), ICD-9 codes 460–519; ICD-10 codes J00–J99	APED meta-analysis of 15 studies published before 2006; coefficient from single-pollutant model  WHO (2013a) noted that the estimates for this pollutant–outcome pair were robust to adjustment to co-pollutants	

## **1.4. Possible double counting of effects of various pollutants**

Quantification of the health impacts of community air pollution in the HRAPIE project focuses on three main pollutants: NO<sub>2</sub>, PM<sub>2.5</sub> and O<sub>3</sub>. In studies of health effects of these pollutants, they are usually correlated to some extent – sometimes negatively so, as with O<sub>3</sub> and PM<sub>2.5</sub> in winter. The REVIHAAP project report therefore proposes quantification of health effects associated with these pollutants only after adjustment for at least one of the others (WHO, 2013a). Far fewer studies systematically applying two- or three-pollutant modelling are available, however, than studies using single-pollutant models. Furthermore, ESs for a given pollutant derived from a multipollutant model may be subject to bias if the pollutants are correlated with each other and subject to measurement error (Fung et al., 1999). This can lead to underestimation of the RR for a pollutant of interest.

The HRAPIE project therefore uses ESs from the largest possible group of studies – i.e. including those from single-pollutant analyses – for quantification. Quantification of the impact for one pollutant from single-pollutant models may to some extent include effects attributable to another. Consequently, for any particular health outcome and exposure period (long-term or short-term exposure), estimated impacts of the three pollutants should not be added without recognizing that addition will, in most practical circumstances, lead to some overestimation of the true impact. Impacts estimated for one pollutant only will, on the other hand, underestimate the true impact of the pollution mixture, if other pollutants also affect that same health outcome.

## **2. Long-term PM exposure**

### **2.1. Effects of long-term PM<sub>2.5</sub> exposure on all-cause mortality**

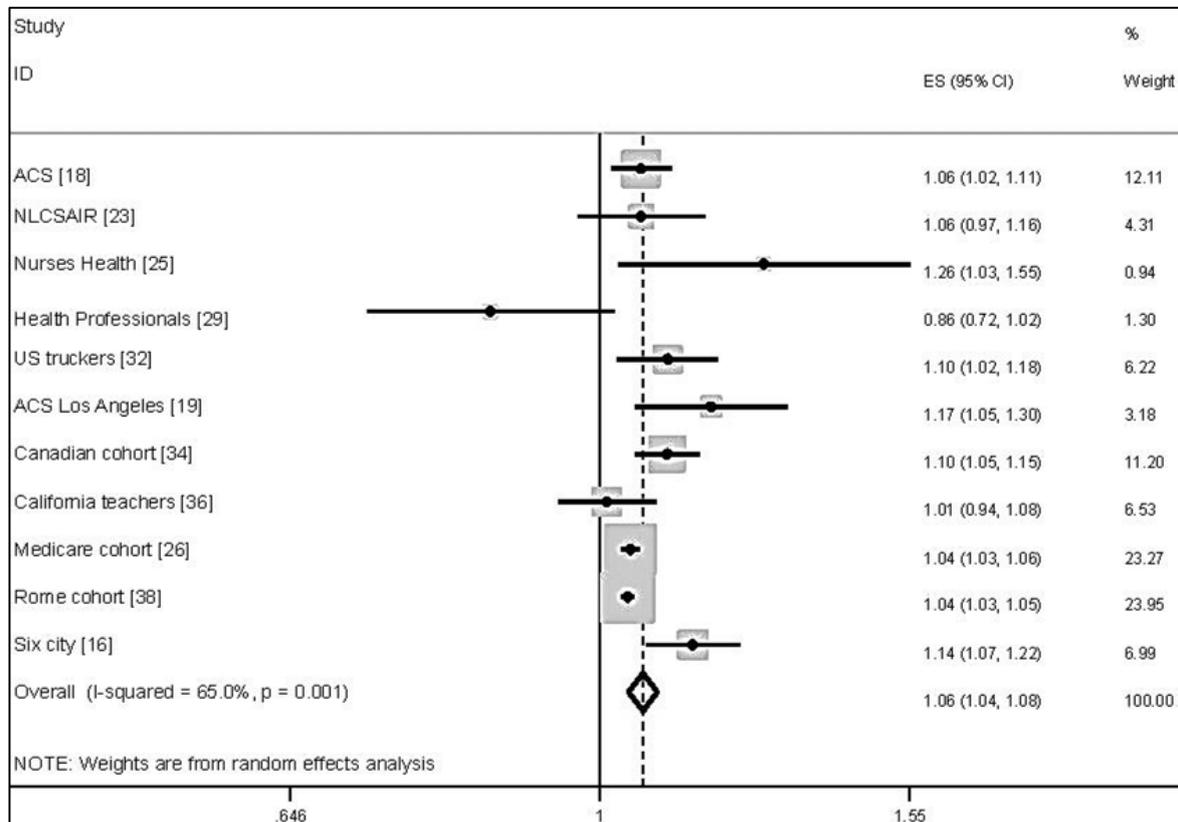
The HRAPIE experts recommended estimation of the impact of long-term (annual average) exposure to PM<sub>2.5</sub> on all-cause (natural) mortality in adult populations (age 30+ years) for cost–effectiveness analysis; this should also be included in Group A\* of the cost–benefit analysis. It should be based on a linear CRF, with an RR of 1.062 (95% CI = 1.040, 1.083) per 10 µg/m<sup>3</sup>. The impacts should be calculated at all levels of PM<sub>2.5</sub>.

The recommended risk coefficient is based on the most recently completed meta-analysis of all cohort studies published before January 2013 by Hoek et al. (2013) (Fig. 1). Thirteen different studies conducted in adult populations of North America and Europe contributed to estimation of this coefficient.

Additional cohort studies on PM and mortality, either all-cause (natural) or cause-specific, have also been published. Differences in exposure assessment or other methods limited their inclusion in the Hoek et al. (2013) quantitative meta-analysis. Some further studies were published after the literature cut-off date of January 2013 (Carey et al., 2013, Kloog et al., 2013), but it is of note that the overall body of evidence is qualitatively consistent with the results of the meta-analysis. Furthermore, there is a wide range of exposure errors in the studies included in the meta-analysis (see Hoek et al., 2013 for details). Studies with a better quality of exposure assessment on average estimated a steeper CRF. It was not possible within the limited timeframe of the HRAPIE project to classify studies by the quality of their

exposure assessment and perform a separate meta-regression to take this into account. The authors therefore acknowledge that the current HRAPIE project recommendation could result in an underestimate of the exposure–response slope.

Fig. 1. Meta-analysis of the association between PM<sub>2.5</sub> and all-cause mortality (RR per 10 µg/m<sup>3</sup>)



Source: Hoek et al. (2013).

Notes: NLCSAIR = Netherlands Cohort Study on Diet and Cancer, air quality investigation section; I-squared refers to the degree of inconsistency across studies.

As noted in IHME (2013), the RR coefficients for both ischaemic heart disease and stroke are modified by age. Whether this effect occurs with ambient air pollution effects on all-cause mortality is unknown because no cohort study has yet identified significant differences in age effects. It has, however, been regarded as prudent, where possible, to make an adjustment for age.

For reasons of simplicity, the Hoek et al. (2013) meta-analysis did not account for this factor. The age structure of EU Member States is similar to that of the groups included in epidemiological studies. Nevertheless, the authors acknowledge that this could theoretically affect the impact estimates based on the Hoek et al. (2013) meta-analysis. The recommended alternative analysis is based on the age-stratified supra-linear exponential decay saturation model applied in the GBD 2010 study (IHME, 2013), which considered only cause-specific mortality.

The PM<sub>2.5</sub> levels observed in these studies correspond to the range expected for the EU in 2020 under the current legislation scenario (not exceeding 20 µg/m<sup>3</sup> in most areas). No

extrapolation beyond the range covered by epidemiological studies on the effects of ambient  $PM_{2.5}$  is needed.

Use of the linear function was discussed in the response and rationale given for question A5 in the REVIHAAP project report, indicating that few of the long-term studies examined the shape of the CRF (WHO, 2013a). The available analyses suggest that it is reasonable to use linear CRFs to assess risks within Europe, given the expected levels of  $PM_{2.5}$  in 2020. This is especially the case for all-cause mortality. For more specific causes of death, a supra-linear function, steeper in lower concentrations, may fit the data slightly better.

The recommendation of all-cause analysis as a primary (A\*) choice and not a set of CRFs for more specific causes of death is supported by two arguments.

- The wider availability of risk estimates, produced by most long-term studies of all-cause mortality, makes them more appropriate for meta-analysis that incorporates a wide range of characteristics specific to the countries included in the analysis. Different groupings of causes of death in various studies make the synthesis of cause-specific results more difficult because of a reduction in the number of eligible studies. Meta-analysis of all-cause mortality can therefore draw on a greater range of studies than would be possible in a cause-specific analysis. A further point is that all-cause mortality includes deaths from causes that might lie outside the cause-specific groups generally reported but are insufficient in cohort studies for individual estimates.
- The background national data on all-cause mortality have greater precision than the cause-specific data. The latter may be affected by misclassification of causes of death in mortality registration across the range of countries included in the analysis (Mathers et al., 2005). As a result, with cause-specific impact estimates, the uncertainty related to background health data will add to the CRF uncertainty, complicating interpretation of the impact assessment.

An additional argument for the use of all-cause mortality is the smaller scale of heterogeneity of the “all-cause” coefficients reported by various epidemiological studies than that observed for cause-specific ones.

Convincing evidence also indicates a relationship between cardiovascular, respiratory and lung cancer mortality and  $PM_{2.5}$  exposure, while many other causes of death (such as gastrointestinal diseases) are less likely to be affected by this air quality parameter. This argument favours cause-specific analysis, recommended as an alternative method (see section 2.2). The HRAPIE experts judged, however, that the frequency of the causes of death linked with exposure was sufficiently similar (between cohorts included in the meta-analysis and between countries in the EU where the impacts are to be estimated) to justify the use of all-cause mortality in the cost–benefit analysis. If the frequency of the causes of death linked with exposure differs markedly between countries, as is the case for global burden estimates, then use of all-cause CRFs will lead to both over- and underestimation of impacts at the country level. This issue should be addressed through comparison of the two alternative methods recommended and in the uncertainty analysis.

The recommendation to assume benefits of any reduction in exposure, including at very low modelled levels of  $PM_{2.5}$ , is based on the assumption that, even after the pollution reduction, the  $PM_{2.5}$  concentration will be likely to exceed the lowest levels observed in recent

epidemiological studies (including because of the natural background). As summarized in the response to question A5, several cohort studies reported effects on mortality at PM<sub>2.5</sub> concentrations well below an annual average of 10 µg/m<sup>3</sup>.

Advantages of the method based on the linear function include its simplicity and independence of the expected health benefits of pollution reduction from the initial level of exposure. It is also important that it follows the approaches applied in the Clean Air for Europe (CAFE) programme in 2005. These are familiar to stakeholders and policy-makers and allow comparison of new results with those from 2005.

Findings from the follow-up of the Harvard Six Cities study suggest that mortality effects may be partially reversible, over a time period possibly as short as a year (Laden et al., 2006; Lepeule et al., 2012). The most appropriate way to express the benefits, identified through cohort studies, of reduced exposure to PM<sub>2.5</sub> is in terms of life-years gained across the population as a whole (COMEAP, 2010; WHO, 2000). As described, for example, in COMEAP (2010), “attributable deaths” are useful for describing the mortality burden in any given year, if some simplifying assumptions are accepted. They are difficult to use, however, in comparing numbers of deaths in a reduced pollution scenario with a baseline long-term scenario, as everyone dies eventually in both cases. Numbers of deaths can be calculated for shorter time periods, but this type of estimate of the impact of exposure is incomplete. Such estimates would also need to be accompanied by a description of the relevant time period, such as “in the first 10 years” (“per year” is not appropriate as the numbers of attributable deaths following a reduction in pollution vary over time as the size and age structure of the population is altered by the additional survivors).

The HRAPIE experts recommended estimation of effects in adult populations (age 30+ years) as most of the evidence providing the CRFs comes from studies that focused on populations around 30 years of age and above.

Baseline mortality rates for the analysis should be based on the data available in the MDB (WHO, 2013c). The rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region for the latest year with available data should be calculated. The data available in the database are compiled from various sources, including a network of country experts; the WHO Regional Office for Europe’s technical programmes; and partner organizations such as United Nations agencies, the statistical office of the EU (EUROSTAT) and the Organisation for Economic Co-operation and Development. The MDB is updated twice a year.

## **2.2. Effects of long-term PM<sub>2.5</sub> exposure on cause-specific mortality**

The cause-specific analysis follows the approach applied in the recently published GBD 2010 study (Lim et al., 2012). It includes an estimation of the effects of long-term exposure to PM<sub>2.5</sub> on mortality from four specific causes of death (cerebrovascular disease, ischaemic heart disease, COPD and lung cancer) in all regions of the world at age 30+ years. This was the preferred approach for the GBD 2010 study because of significant differences in the structure of reporting of causes of death between regions (IHME, 2013). The PM<sub>2.5</sub> levels considered in the GBD 2010 study expanded far beyond the concentrations observed in long-term epidemiological studies on the effects of ambient air pollution conducted in North America and western Europe, so the estimation of CRFs integrated results of studies on

ambient air pollution with those of studies on effects of PM from second-hand smoke, indoor air pollution from household solid fuel use, and active smoking, following the approach published by Pope et al. (2011). This approach assumes that the health impacts of fine PM from various sources are similar. It avoids estimation of unrealistically high risks in populations exposed to very high ambient levels of PM<sub>2.5</sub> (those much higher than in Europe), which could result from linear or even logarithmic extrapolation of the results of studies on effects of ambient air quality.

The CRFs applied in the GBD 2010 study (IHME, 2013) were based on a three-parameter exponential decay saturation model with a power of PM<sub>2.5</sub> concentration. The approach to developing this model is described in the response and rationale given for question D4 in the REVIHAAP project report (WHO, 2013a) and a paper providing a more detailed model description is in preparation. This model provided the best overall fit among all four health outcomes studied, compared to the seven alternative models examined. The CRFs reflect a steeper increase in risk at low exposure levels than that for higher exposures (supra-linear function) observed in some epidemiological studies. The estimates of risk based on this approach compare well with the results of a recent study conducted in China (Cao et al., 2011), with estimated PM<sub>2.5</sub> (converted from total suspended particles) concentrations ranging from 38–166 µg/m<sup>3</sup>.

The REVIHAAP project recommended the GBD 2010 approach for cost–benefit analysis, noting that its application would involve a linearization of the CRFs, using the PM<sub>2.5</sub> level expected in 2020 under the current legislation scenario. In practice, estimates were sensitive to assumptions about the level below which effects would not be quantified; this was one reason the GBD 2010 cause-specific values do not contribute to the total effect but are recommended as an alternative to all-cause mortality.

As noted in section 2.1, epidemiological studies of risk factors for both ischaemic heart disease and stroke indicate that the RR declines with the logarithm of age (Lim et al., 2012). The HRAPIE experts therefore recommended calculation of both age-specific and all-age estimates to assess the potential effect of stratification. The matrix of risk coefficients (by baseline PM<sub>2.5</sub> level and age, for each of the outcomes) is provided in the GBD 2010 study.

Furthermore, the International Agency for Research on Cancer (IARC) recently classified ambient air pollution in general, and PM specifically, as a Group 1 carcinogen (IARC, 2013). Future health impact assessment and cost–benefit analysis exercises should consider recommendations for PM<sub>2.5</sub> and lung cancer incidence (besides lung cancer mortality), as this outcome contributes to the burden of disease of air pollution. In view of the HRAPIE project timeline, however, a formal meta-analysis for this outcome was not undertaken, and specific recommendations for lung cancer incidence were not made. The proposed recommendations for all-cause and cause-specific mortality (which include lung cancer as a cause of death) are thought partially to cover this outcome, but as they relate only to lung cancer mortality and not to development of cancer, this may lead to a small underestimation of the effects.

As for all-cause mortality, the calculation of life-years gained is more appropriate than numbers of deaths although it is possible to have long-term changes in numbers of deaths from specific causes. Again as for all-cause mortality, the duration of follow-up in life tables needs to be defined (such as, for example, the lifetime of those at the start of the policy change); this is particularly important for lung cancer, where a short lag would be

inappropriate and a short follow-up would miss the effect. Baseline rates for mortality should be sourced from the European detailed mortality database (WHO, 2013d).

### **2.3. Effects of long-term PM<sub>10</sub> exposure on postneonatal mortality**

For infant mortality, the HRAPIE experts recommended using the results of the study by Woodruff, Grillo and Schoendorf (1997), based on 4 million infants in the United States. The endpoint was postneonatal infant mortality, defined as death between the ages of 1 and 12 months. The associations reported in the study between all-cause mortality and PM<sub>10</sub> (measured as the average during the first two months of life) generated an RR of 1.04 (95% CI = 1.02, 1.07) per 10 µg/m<sup>3</sup> PM<sub>10</sub>. This study is preferred over a more recent study (Woodruff, Darrow and Parker, 2008) of 3.5 million infants in the United States, which reports associations with respiratory-specific postneonatal infant mortality. While this later study provides general support for infant mortality effect from long-term exposure, data on the cause-specific postneonatal mortality are not available in international databases. Further studies, mostly in developing countries, provide additional support for an effect of acute exposure to PM (Cohen et al., 2004).

Country-specific postneonatal mortality rates should be used, based on the European Health for All database (WHO, 2013e), possibly including United Nations projections, as background data.

These recommendations are based on a limited number of studies only and, owing to the limited resources of the current project, were prepared without a formal systematic review of the evidence on the impact of PM on postneonatal mortality. The confidence in quantitative estimate of risk is considered to be moderate, and the pollutant–outcome pair is recommended for inclusion in Group B\*.

### **2.4. Effects of long-term PM<sub>10</sub> exposure on prevalence of bronchitis in children**

The CRF for this endpoint is taken from the PATY study (Hoek et al., 2012), which analysed data collected by cross-sectional studies previously conducted in 11 countries. Data on “bronchitis in the past 12 months” were available from about 40 000 children aged 6 to 12 years living in nine countries, with most subjects living in European cities. A borderline significant association of bronchitis prevalence with long-term average PM<sub>10</sub> concentration in cities was reported with an ES of 1.08 (95% CI = 0.98, 1.19) per 10 µg/m<sup>3</sup> annual mean PM<sub>10</sub>. The analysis found evidence for heterogeneity of the association ( $p < 0.10$ ) between the studies, possibly related to the differences in design of individual studies included in the PATY study and diagnostic differences affecting bronchitis definition. This outcome contributes to the calculation of RADs, so when the total burden of disease and costs due to PM are calculated, RADs should be reduced accordingly.

In the cost–benefit analysis, this estimate is to be applied to all children aged 6–12 years (or 6–18 years if only this age category is available). The baseline rate of bronchitis in the previous 12 months can be based on the results of the PATY study. Although the estimates from various countries ranged from 6.2% to 41.5%, the HRAPIE experts recommended the mean prevalence rate of 18.6% from the PATY study for the analysis. The pollutant–outcome pair is recommended for inclusion in Group B\*.

## 2.5. Effects of long-term PM<sub>10</sub> exposure on incidence of chronic bronchitis in adults

The recommended estimate of CRF for chronic bronchitis is based on two studies: the AHSMOG study from California, United States (Abbey et al., 1995a; 1995b) and SAPALDIA from Switzerland (Schindler et al., 2009). Both conducted longitudinal analyses in which the probability of a new case of chronic bronchitis over an approximately 10-year inter-survey period was related to PM over the same period, adjusting for other factors. Within this framework, the two studies used different exposure metrics: the results in the AHSMOG study are for the average annual mean concentration of PM<sub>2.5</sub> over the inter-survey period (1966–1977), whereas SAPALDIA found relationships with the change in annual mean PM<sub>10</sub> over the inter-survey period (1991–2002). Both studies defined chronic bronchitis similarly, as having had symptoms of cough and/or sputum production on all or most days, for at least three months per year for at least two years. For monetary valuation, note that this is milder than the often-used requirement of chronic cough *and* sputum.

The AHSMOG study used a cohort of about 3900 non-smokers above the age of 28 years for the first survey. Estimated lifetime exposures over a 20-year period were assigned based on detailed history of both work and residential location via two approaches. Using exposures in PM<sub>10</sub> derived from total suspended particles measurements, Abbey et al. (1995a) estimated an RR which gave an estimated change of 7.0% (95% CI = -0.5%, 14.3%) in new cases per 10 µg/m<sup>3</sup> PM<sub>10</sub>. The CAFE programme analysis (Hurley et al., 2005) used this estimate of risk, for which the CI was derived. Using exposures to PM<sub>2.5</sub> based on airport visibility data, Abbey et al. (1995b) generated an ES of 14% (95% CI = -0.45%, 26.2%) change in new cases per 10 µg/m<sup>3</sup> of PM<sub>2.5</sub>. The HRAPIE experts preferred this second study, since there is much more uncertainty in estimating PM<sub>10</sub> in multiple cities from total suspended particles than in directly estimating PM<sub>2.5</sub> from airport visibility in each city where good model fits were obtained.

Schindler et al. (2009) provide support for the higher estimate of the two RRs from the AHSMOG study. This study examined relationships between chronic bronchitis and the change in modelled concentrations of PM<sub>10</sub> in the residence in about 7000 adults aged 16–60 years, at first survey residing in eight communities in Switzerland. This study estimated an odds ratio of 0.78 (95% CI = 0.62, 0.98), equivalent to a decrease of risk of new reports of chronic bronchitis by 22% (95% CI = 2%, 38%) per 10 µg/m<sup>3</sup> decrease in PM<sub>10</sub>.

Converting the results of the Abbey et al. (1995b) study to PM<sub>10</sub> units (assuming PM<sub>2.5</sub>/PM<sub>10</sub> = 0.65) and using an inverse-variance weighted average of that study with the results of the Schindler et al. (2009) study obtains an RR for chronic bronchitis of 1.117 (95% CI = 1.040, 1.189) per 10 µg/m<sup>3</sup> PM<sub>10</sub>.

Schindler et al. (2009) also looked at all the subjects in the cohort reporting symptoms that can be explained by air pollution, at the end of the inter-survey period. The study reveals a substantial dynamic of change in those symptoms, with many not reporting the symptoms in a second survey, others reporting new ones, and a smaller group reporting symptoms at both surveys. To avoid overestimating the overall attributable burden the HRAPIE experts propose to restrict the assessment to quantifying the air pollution-associated burden for reporting symptoms at follow-up while being free of symptoms at baseline. Given the dynamics of

bronchitis, as defined by questionnaire methods, some of those incident cases will be free of symptoms sometime in the future, while others will suffer from a more persistent symptomatology.

In the absence of country-specific baseline rates for chronic bronchitis, the HRAPIE experts recommended using the estimates from the AHSMOG study and SAPALDIA, which provide the RRs. Adjusting for remission, and following the United States Environmental Protection Agency’s Environmental Benefits Mapping and Analysis programme, the baseline incidence rate from AHSMOG is 3.78 incident cases annually per 1000 adults at risk. Analysis of Schindler et al. (2009), again adjusting for remission, gave a remarkably similar value for SAPALDIA of 3.9 cases per 1000 adults at risk who reported symptoms at the second survey but not at baseline.

These recommendations are based on two studies only and, owing to the limited resources of the current project, were prepared without a formal systematic review of the evidence on the impact of PM on chronic bronchitis incidence. A recently published systematic review of studies on the relationship of COPD to air pollution (Schikowski et al., 2013) could offer support. Chronic bronchitis, defined on the basis of reported symptoms of cough and phlegm, is considered a rather weak indication of clinically recognized COPD diagnosed on the basis of spirometry or clinical examination, but such symptoms are known predictors of objectively defined future COPD. The Schikowski et al. (2013) study used objective measures (namely spirometry) or ICD codes in the hospital discharge or death record. It concluded that the evidence of long-term effects of air pollution on the prevalence and incidence of COPD among adults was suggestive but not conclusive, despite plausible biological mechanisms and good evidence that air pollution affects lung development in childhood and triggers exacerbations in COPD patients.

Based on this conclusion and the possibly incomplete evidence on CRF for chronic bronchitis used in the current analysis, quantification of the effects of PM<sub>10</sub> on chronic bronchitis incidence is recommended for inclusion in Group B\*, for which there is less certain supportive evidence and less confidence in the CRF. Unresolved difficulties also exist in combining and using coefficients from a study of PM level with those of a study of change in PM level, and this is a further reason for recommending that this pollutant–outcome pair should be included in Group B\*.

### **3. Short-term PM exposure**

#### **3.1. Effects of short-term PM<sub>2.5</sub> exposure on all-cause mortality**

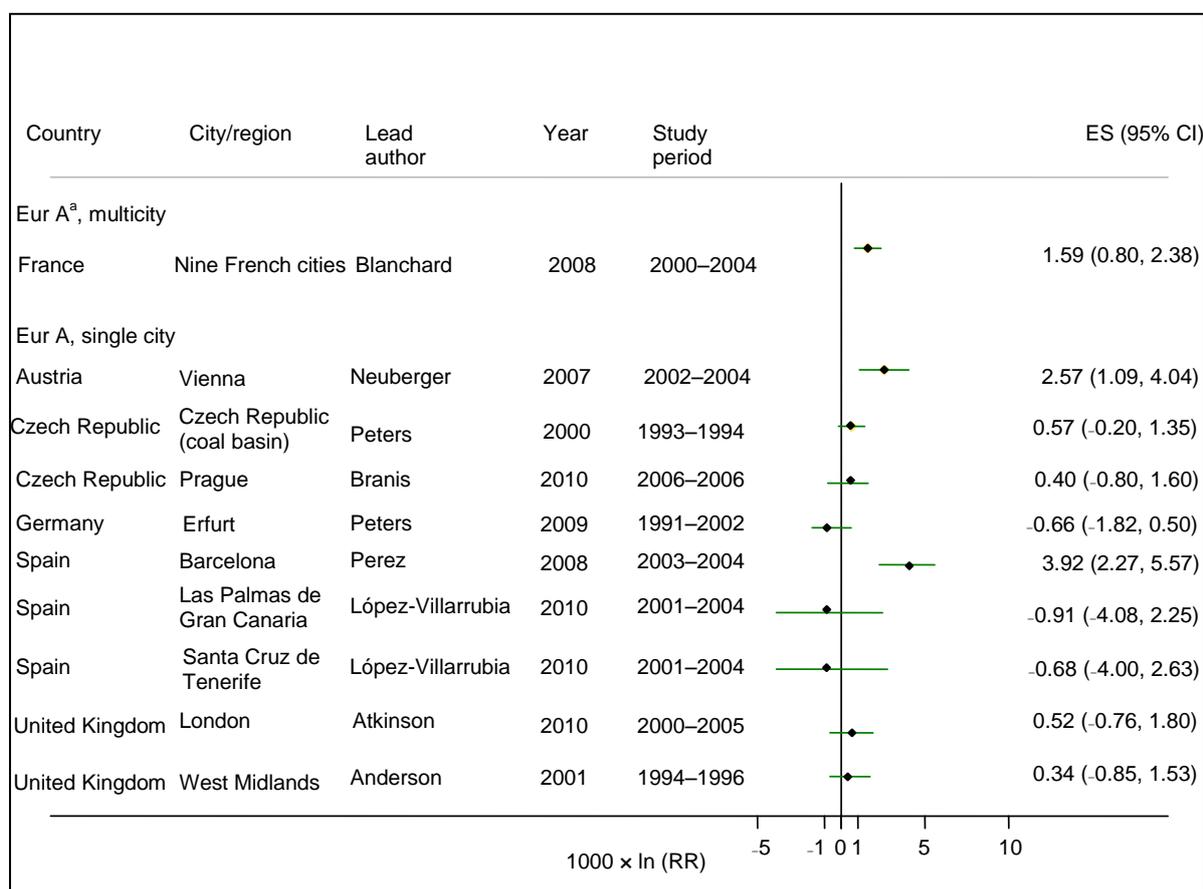
The HRAPIE experts expressed concern that the premature deaths attributed to short-term changes of PM<sub>2.5</sub> concentration were already accounted for in estimations of the effects of long-term exposure. They therefore recommended that quantification of the effects of short-term exposure should be done for information only; it is not proposed as an alternative to quantification of long-term PM<sub>2.5</sub> exposure.

The APED meta-analysis included results of 12 single-city time-series studies and one multicity study on all-cause mortality for all ages. Single-city (or region) results were for Vienna, Austria (Neuberger, Rabczenko and Moshhammer, 2007); the coal basin (Peters et al.,

2000) and Prague (Branis et al., 2010) in the Czech Republic; Erfurt, Germany (Peters et al., 2009); Barcelona (Perez et al., 2008), Las Palmas de Gran Canaria and Santa Cruz de Tenerife (López-Villarrubia et al., 2010) in Spain; and London (Atkinson et al., 2010) and the West Midlands in the United Kingdom (Anderson et al., 2001). The multicity study reported results from an analysis of nine French cities (Blanchard, 2008) (Fig. 2). The random effects summary estimate, expressed as the percentage increase in the mean number of deaths for a  $10 \mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{2.5}$ , was 1.23% (95% CI = 0.45%, 2.01%). The individual estimates were robust on adjustment for other pollutants.

While additional evidence published since May 2011 is not included in this review, a recent multicity study in 10 European Mediterranean metropolitan areas (including Barcelona) – the MED-PARTICLES project (Samoli et al., 2013) – found an increase in daily mortality of 0.55% (95% CI = 0.27%, 0.84%) associated with a  $10 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$ .

Fig. 2. Risk estimates for  $\text{PM}_{2.5}$  and all-cause mortality, all ages



Source: work funded by and reproduced with permission of the United Kingdom Department of Health Policy Research Programme.

<sup>a</sup> The WHO European Region EUR A countries are: Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

Two large multicity studies of  $\text{PM}_{2.5}$  and all-cause mortality were also undertaken in Canada and the United States. Burnett et al. (2004) studied daily mortality in 12 Canadian cities and reported an RR (expressed as a percentage) of 0.60% (95% CI = -0.03%, 1.23%) per  $10 \mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{2.5}$ . In the United States, Zanobetti and Schwartz (2009) found a

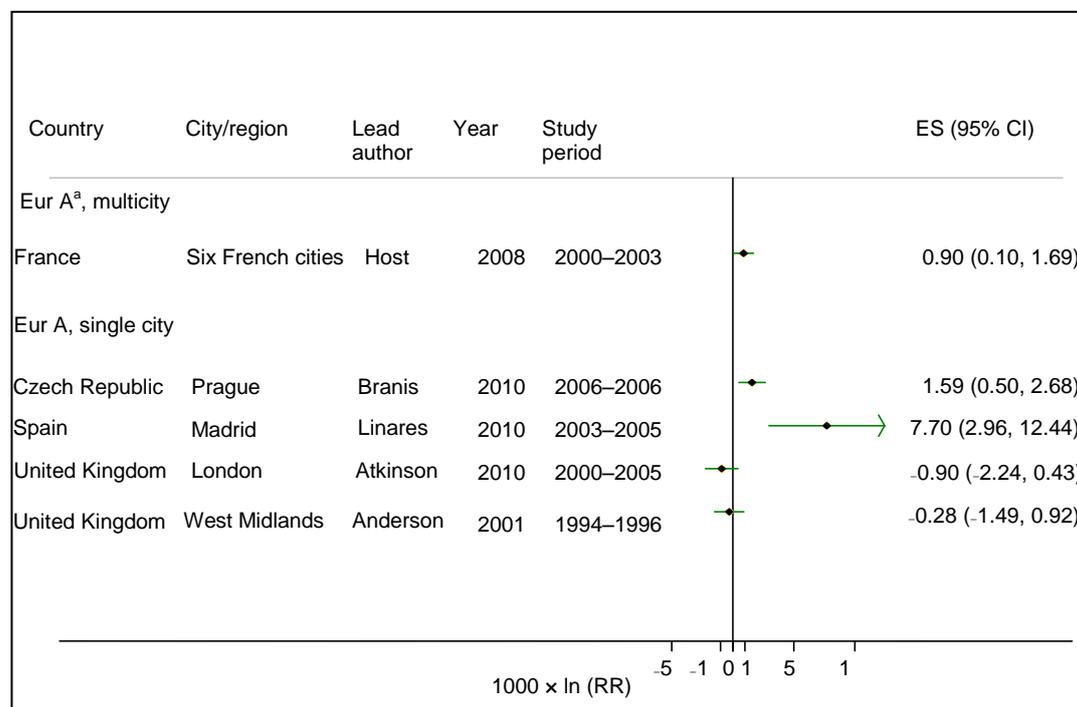
stronger association in their study of 112 cities of 0.98% (95% CI = 0.75%, 1.21%), also per 10  $\mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{2.5}$ . Both these pooled estimates are smaller than the summary estimate from Europe, although their CIs overlap substantially with the European pooled estimate. These studies, conducted in developed countries with comparable sources of fine particle pollution to European countries, provide support for evidence of an association between  $\text{PM}_{2.5}$  and mortality observed in Europe.

The time-series studies provide support for the use of evidence from cohort studies for cost–benefit analysis. Effects should be calculated at all PM levels. Baseline rates for mortality should be sourced from the MDB (WHO, 2013c), which provides mortality indicators stratified by 67 causes of death, age and sex.

### 3.2. Effects of short-term $\text{PM}_{2.5}$ exposure on hospital admissions for CVDs and respiratory diseases

The APED meta-analysis of studies of  $\text{PM}_{2.5}$  and CVD hospital admissions in Europe used results from five studies of subjects of all ages: a multicity study of six French cities (Host et al., 2008) and single-city (or region) studies from Prague (Branis et al., 2010), Madrid (Linares and Diaz, 2010), London (Atkinson et al., 2010) and the West Midlands (United Kingdom) (Anderson et al., 2001) (Fig. 3). The random effects summary estimate calculated was 0.91% (95% CI = 0.17%, 1.66%) per 10  $\mu\text{g}/\text{m}^3$ .

Fig. 3. Risk estimates for short-term  $\text{PM}_{2.5}$  and hospital admissions for CVDs, all ages



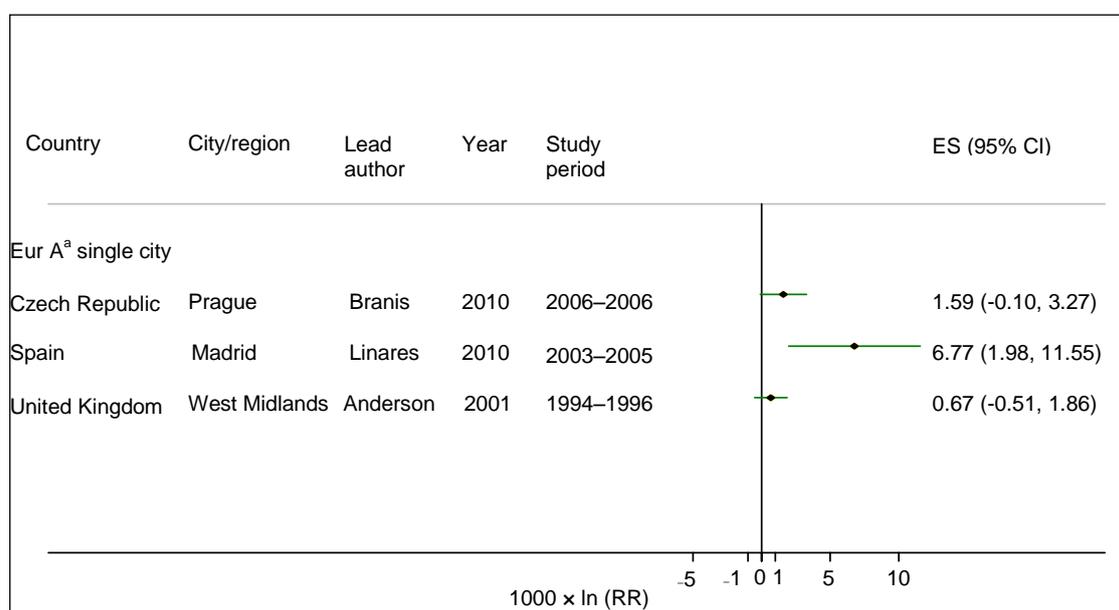
Source: work funded by and reproduced with permission of the United Kingdom Department of Health Policy Research Programme.

<sup>a</sup> The WHO European Region EUR A countries are: Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

Three single-city studies conducted in Prague (Branis et al., 2010), Madrid (Linares and Díaz, 2010) and the West Midlands (United Kingdom) (Anderson et al., 2001) also reported results for hospital admissions for all-age respiratory disease (Fig. 4). The random effects summary estimate calculated was 1.90% (95% CI = -0.18%, 4.02%) per 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$ .

While additional evidence published since May 2011 is not included in this review, the authors note data for hospital admissions in eight Mediterranean cities from the MED-PARTICLES project (Stafoggia et al., 2013). This study reported increases in daily admissions for CVDs and respiratory diseases (in subjects aged 15+ years) of 0.43% (95% CI = 0.04%, 0.83%) and 1.25% (-0.02%, 2.54%) respectively per 10  $\mu\text{g}/\text{m}^3$  increases in  $\text{PM}_{2.5}$ . The CRFs are based on European studies but the investigations conducted in other regions, as reviewed in the REVIHAAP project report (WHO, 2013a), provide qualitative support.

Fig. 4. Risk estimates for short-term  $\text{PM}_{2.5}$  and hospital admissions for respiratory diseases, all ages



Source: work funded by and reproduced with permission of the United Kingdom Department of Health Policy Research Programme.

<sup>a</sup> The WHO European Region EUR A countries are: Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

Baseline hospitalization rates should be taken from the European hospital morbidity database (WHO, 2013f). The hospitalizations contribute to the calculation of RADs, so when the total burden of disease and costs due to PM are calculated, RADs should be reduced accordingly. The pollutant–outcome pairs are recommended for inclusion in Group A\*.

### 3.3. Effects of short-term $\text{PM}_{2.5}$ exposure on RADs

RADs include days when individuals reduce their normal activities, including days of missed work, absences from school and other more minor reductions in daily activity. As a result, calculation of RADs is likely to incorporate many of the lower respiratory symptoms, as well as other relatively minor outcomes associated with PM in previous research such as doctor

visits, medication use and lower and upper respiratory symptoms (Ward and Ayres, 2004; Hoek and Brunekreef, 1995). The effects of PM on work days lost, hospitalizations and asthmatic symptoms in children contributing to the RADs can be estimated according to the methods recommended in the other sections. These more specific outcomes should not be added to RADs to avoid double counting of effects.

Only one study is available that can inform the HRAPIE project’s recommendations. The CRF for RADs is based on a study of six years of data from the United States National Health Interview Survey (Ostro, 1987), which included approximately 12 000 adults (aged 18–64 years) each year from 49 metropolitan areas of the United States. The relationship between two-week average  $PM_{2.5}$ <sup>1</sup> and RADs was estimated for each year individually with ESs ranging from 2.8% to 9% per  $10 \mu\text{g}/\text{m}^3$   $PM_{2.5}$ . A meta-analysis using inverse-variance weighting generates an overall estimate of 4.7% (95% CI = 4.2%, 5.3%) change in RADs per  $10 \mu\text{g}/\text{m}^3$   $PM_{2.5}$ . The HRAPIE experts recommended applying this CRF to all age groups, given the likelihood of similar or greater effects of  $PM_{2.5}$  on RADs for those aged under 18 and over 64 years. Support for this assumption is provided by the United Kingdom General Lifestyle Survey of 2008, which reported on the number of RADs experienced by individuals in the United Kingdom population (Ali et al., 2010), finding approximately 23 RADs per person per year, with 17 RADs per person in the 16–44 age group and 32 RADs per person in the 45–64 age group. These results are supported by data for the United States National Health Interview Survey (Adams and Marano, 1994), which show restrictions resulting from acute conditions (Table 2; RADs resulting from chronic conditions are not included in the table but are in the original epidemiological study).

Table 2. RADs resulting from acute conditions

Age group	Average number of RADs per year
<5	8.76
5–17	6.33
18–24	6.39
24–44	6.64
45–64	6.30
65+	8.95

Source: Adams and Marano (1994).

In the absence of national data on RADs, the HRAPIE experts recommended using the baseline rate of RADs of 19 per person per year, as in the Ostro and Rothschild (1989) study. Fairly similar rates were observed for the Canadian population (Stieb et al., 2002) and that of the United Kingdom (Ali et al., 2010).

This pollutant–outcome pair is recommended for inclusion in Group B\*. Only the residual RADs should be added to the total effect, however, after days in hospital, work days lost and days with symptoms are accounted for.

### 3.4. Effects of short-term $PM_{2.5}$ exposure on work days lost

The CRFs for this endpoint are also based on the Ostro (1987) study (see section 3.3). The meta-analysis for work days lost generates a CRF of 4.6% (95% CI = 3.9%, 5.3%) change

<sup>1</sup> Assuming linearity, the health effects of daily variations in  $PM_{2.5}$  can be calculated using another averaging time, such as daily or annual average.

per 10  $\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ , applied to all current workers. For baseline rates, country-specific data on absenteeism from work due to illness is provided by the European Health for All database (WHO, 2013e). Although baseline rates are available for most countries, the definitions and criteria used for registering sick leave differ significantly between countries, increasing the uncertainty of burden estimates.

The burden of work days lost (in terms of either disability-adjusted life-years or economic costs) should not be added to the burden of RADs because of the clear overlap in the groups of people affected. The estimated number of work days lost should therefore be subtracted from the estimated number of RADs to avoid double counting before burden calculations, and should also be quantified separately.

### **3.5. Effects of short-term $\text{PM}_{10}$ exposure on incidence of asthma symptoms in asthmatic children**

For this endpoint the HRAPIE experts used the meta-analysis of 36 panel studies of asthmatic children aged 5–19 years (Weinmayr et al., 2010). The studies were conducted in 51 populations, including 36 from Europe, with the children’s pre-existing asthmatic status confirmed by a physician or by reporting relevant symptoms or medication through a questionnaire. The definition of occurrence of asthma symptoms varied by study and included coughing, wheezing, shortness of breath, asthma attacks or asthma symptoms. Using a random effects analysis to address the heterogeneity between the studies, an effect of 2.8% (95% CI = 0.6%, 5.1%) for a 10  $\mu\text{g}/\text{m}^3$  change in daily  $\text{PM}_{10}$  was estimated.

In the cost–benefit analysis, this CRF should be applied to asthmatics aged 5–19 years. The prevalence of asthma in children based on “severe asthma” in ISAAC (Lai et al., 2009) is 4.9% for western Europe and 3.5% for northern and eastern Europe. Based on interpolation of data from several panel studies, the daily incidence of symptoms in this group is assumed to be 17% (Peters et al., 1997; Segala et al., 1999; van der Zee et al., 1999).

The burden of asthma symptoms (in terms of either disability-adjusted life-years or economic costs) should not be added to the burden of RADs because of the clear overlap in the groups of people affected. The estimated number of days with asthma symptoms should therefore be subtracted from the estimated number of RADs to avoid double counting before burden calculations.

## **4. Long-term $\text{O}_3$ exposure**

### **4.1. Effects of long-term $\text{O}_3$ exposure on respiratory mortality**

The recommended CRFs are based on analyses of the data collected in the ACS cohort, including subjects aged 30+ years at the start of the follow-up. At least some proportion of the short-term effects on mortality is likely to be included in the estimated number of effects of long-term exposure. The HRAPIE experts therefore recommended inclusion of this pollutant–outcome pair as an alternative to the effects of short-term  $\text{O}_3$  on mortality in Group B (not contributing to the total effect of the extended set).

Estimation of impacts on respiratory mortality in people aged 30+ years uses RR coefficient 1.014 (95% CI = 1.005, 1.024) per 10  $\mu\text{g}/\text{m}^3$  of the summer months (April–September) average of daily maximum 8-hour mean  $\text{O}_3$  concentration. This coefficient is derived from the single-pollutant analysis of ACS data in 96 metropolitan statistical areas of the United States (Jerrett et al., 2009a). It is re-scaled from 1-hour means to 8-hour means using a ratio of 0.72, derived from the APHEA-2 project (Gryparis et al., 2004).

The risk coefficients should be applied to summer months mean 8-hour  $\text{O}_3$  concentrations above 35 ppb. This cut-off point results from the fact that summer months mean  $\text{O}_3$  concentration exceeded 35 ppb in most areas included in the ACS analysis, so no information exists on the shape of the CRF below that level. The MDB (WHO, 2013c) should be used to provide the baseline number of deaths for all 53 countries of the WHO European Region.

## 5. Short-term $\text{O}_3$ exposure

### 5.1. Effects of short-term $\text{O}_3$ exposure on all-cause mortality

The HRAPIE experts recommended that this analysis should be included in both the cost–effectiveness and the cost–benefit analysis. It includes estimates of the impact of short-term (daily maximum 8-hour mean) exposure to  $\text{O}_3$  on all-cause mortality for all ages. The impacts of  $\text{O}_3$  should be calculated according to the linear function with RR coefficient 1.0029 (95% CI = 1.0014, 1.0043) per 10  $\mu\text{g}/\text{m}^3$ .

The recommended risk coefficients are based on data from 32 European cities included in the APHENA study and discussed in more detail in the REVIHAAP project report in the response and rationale given for question B1 (WHO, 2013a). The coefficients for the daily maximum 8-hour mean  $\text{O}_3$  concentrations were derived from the coefficients for the 1-hour means published in the APHENA study report (Katsouyanni et al., 2009). They were re-scaled from 1-hour means to 8-hour means using a ratio of 0.72, derived from the APHEA-2 project (Gryparis et al., 2004). The recommended coefficients are adjusted for  $\text{PM}_{10}$  (to avoid or reduce double counting).

For the cost–effectiveness analysis, the HRAPIE experts recommended a cut-off concentration of 35 ppb (70  $\mu\text{g}/\text{m}^3$ ) to reflect greater confidence in the significant relationship above 35 ppb. An additional argument is the availability of  $\text{O}_3$  models that can estimate the sum of means over 35 ppb with greater reliability than concentrations below 35 ppb. Owing to uncertainty regarding the presence of a threshold for  $\text{O}_3$  effects, additional effort to estimate the impacts of  $\text{O}_3$  in concentrations above 10 ppb, which is the lowest concentration observed in monitoring stations in Europe (using the sum of means over 10 ppb), would also be justified. In such additional analysis, the same risk coefficients should be used as with the sum of means over 35 ppb.

It should be noted that the coefficients in the APHENA study were based on the whole range of observed  $\text{O}_3$  concentrations, including levels below 35 ppb. No assumption of “no effect” of the lower levels of  $\text{O}_3$  is thus made in the impact calculations. Rather, any such impacts are ignored in the cost–effectiveness analysis. While this approach should not affect comparison of various policies reducing peaks of  $\text{O}_3$ , the effect of this assumption should be tested in the cost–benefit analysis.

The MDB (WHO, 2013c) should be used to provide number of deaths for all 53 countries of the WHO European Region, for the latest year with available data. The data are compiled from various sources, including a network of country experts; the WHO Regional Office for Europe’s technical programmes; and partner organizations such as agencies of the United Nations system, EUROSTAT and the Organisation for Economic Co-operation and Development. The MDB is updated twice a year.

## 5.2. Effects of short-term O<sub>3</sub> exposure on cardiovascular and respiratory mortality

The impacts of O<sub>3</sub> in concentrations above 35 ppb (70 µg/m<sup>3</sup>) maximum daily 8-hour means – using the sum of means over 35 ppb – should be calculated according to the linear function with RR coefficients 1.0049 (95% CI = 1.0013, 1.0085) per 10 µg/m<sup>3</sup> for cardiovascular and 1.0029 (95% CI = 0.9989, 1.0070) for respiratory mortality. The source of these coefficients is the APHENA study, which also provided the risk function for all-cause core analysis (Katsouyanni et al., 2009). Coefficients for cardiovascular mortality for all ages were calculated using a weighted average of the results for ages 75+ years and <75 years, based on the proportion of subjects in the European population aged 75+ years (6.4% calculated as the mean of the city-specific proportions) in the APHENA study.

Additional analysis for O<sub>3</sub> concentrations above 20 µg/m<sup>3</sup> (10 ppb) – using the sum of means over 10 – should also be performed. The MDB (WHO, 2013c) should be used to provide the number of deaths for all 53 countries of the WHO European Region.

## 5.3. Effects of short-term O<sub>3</sub> exposure on hospital admissions for CVDs and respiratory diseases

The APHENA study analysed associations between O<sub>3</sub> (maximum 1 hour) and hospital admissions (Katsouyanni et al., 2009). In Europe, data were available from eight cities and stratified by respiratory disease and CVDs (cardiac) in subjects aged 65+ years (Table 3). The findings of the APHENA study provide the most comprehensive overview of the evidence for an association between O<sub>3</sub> and hospital admissions for respiratory and cardiac diseases in Europe. Results from the United States and Canada are included in Table 3 for comparative purposes. The HRAPIE experts note the inconsistency in the results between regions when O<sub>3</sub> estimates are adjusted for PM<sub>10</sub>: this weakens the evidence for an association between O<sub>3</sub> and hospital admissions observed in Europe.

Table 3. Pooled estimates for hospital admissions for respiratory and cardiac diseases

Outcome	Europe (eight cities)		United States		Canada	
	Single pollutant	Adjusted for PM <sub>10</sub>	Single pollutant	Adjusted for PM <sub>10</sub>	Single pollutant	Adjusted for PM <sub>10</sub>
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Cardiac, 65+ years	-0.10 (-0.46, 0.27)	0.64 (0.36, 0.91)	0.10 (-0.11, 0.31)	-0.04 (-0.28, 0.19)	0.26 (-0.2, 0.73)	0.63 (-0.22, 1.5)
Respiratory, 65+ years	0.19 (-0.28, 0.67)	0.32 (0.05, 0.60)	0.18 (-0.12, 0.49)	0.08 (-0.26, 0.41)	0.74 (-0.05, 1.5)	0.39 (-1.1, 1.9)

Source: based on Katsouyanni et al., 2009.

Note: Figures reported are percentage increases in admissions (95% CI) per 10 µg/m<sup>3</sup> increment in daily maximum 1-hour O<sub>3</sub> concentrations.

Following the REVIHAAP project’s recommendations, the cost–benefit analysis should be based on the daily maximum 8-hour mean (WHO, 2013a). This was re-scaled from 1-hour means to 8-hour means using a ratio of 0.72, derived from the APHEA-2 project (Gryparis et al., 2004). The risk coefficients per 10  $\mu\text{g}/\text{m}^3$  daily maximum 8-hour mean scaled from the APHENA estimates adjusted for  $\text{PM}_{10}$  (Table 3), are as follows:

- for cardiovascular admissions (age 65+ years): 0.89% (95% CI = 0.50%, 1.27%)
- for respiratory admissions (age 65+ years): 0.44% (95% CI = 0.07%, 0.83%).

Impact estimates of the sum of means over 10 ppb and the sum of means over 35 ppb (daily maximum 8-hour) should be calculated.

The baseline numbers of hospital admissions for each country should be taken from the European hospital morbidity database (WHO, 2013f) (number of discharges for all ages minus numbers for ages 0–14 and 14–64 years).

#### **5.4. Effects of short-term $\text{O}_3$ exposure on MRADs**

An RAD is a day when individuals reduce their normal activities, for health-related reasons. MRADs do not involve work loss or bed disability, but do include some noticeable limitation on “normal” activity.

The recommended CRF is based on the Ostro and Rothschild (1989) study, which carried out six separate analyses of annual data of the United States National Health Interview Survey 1976–1981, examining relationships between respiratory RADs or MRADs and  $\text{O}_3$  (2-week averages of daily 1-hour maximum,<sup>2</sup> in  $\mu\text{g}/\text{m}^3$ ) or  $\text{PM}_{2.5}$  (same data as for Ostro, 1987 – see sections 3.3 and 3.4). Perhaps surprisingly, there was no clear or consistent relationship linking  $\text{O}_3$  and respiratory RADs. There was, however, a reasonably strong and consistent relationship between MRADs and  $\text{O}_3$ .

Direct evidence on  $\text{O}_3$  exposure and symptoms in clinical and panel studies was discussed in the REVIHAAP project report and supports the plausibility of MRADs (WHO, 2013a). The study by Ostro and Rothschild (1989) was used in the CAFE programme; the HRAPIE experts propose that the same relationship should be used again and that – as in the CAFE programme – this is also used as a surrogate for minor symptoms, to avoid double counting. The following short description draws heavily on the CAFE programme cost–benefit analysis methodology report (Hurley et al., 2005).

Ostro and Rothschild (1989) reported results for single- and two-pollutant models, adjusting for city differences and various individual-level socioeconomic confounders. Following the CAFE programme, the HRAPIE experts used the two-pollutant results: the regression coefficients for  $\text{O}_3$  were also adjusted for  $\text{PM}_{2.5}$ . The regression coefficients for the six individual years were very variable, with most (including two negative) being statistically significant individually. The weighted mean was derived as 0.00111 (standard error (SE) 0.00034), giving an increase of 0.111% (95% CI = 0.043%, 0.179%) per  $\mu\text{g}/\text{m}^3$   $\text{O}_3$  (1-hour

---

<sup>2</sup> Assuming linearity, the health effects of daily variations in  $\text{O}_3$  can be calculated using another averaging time, such as daily or annual average.

maximum) or 1.54% (95% CI = 0.60%, 2.49%) per 10  $\mu\text{g}/\text{m}^3$   $\text{O}_3$  (daily 8-hour average). This was re-scaled from 1-hour means to 8-hour means using a ratio of 0.72, derived from the APHEA-2 project (Gryparis et al., 2004).

The original study only included current workers resident in urban areas. As with  $\text{PM}_{2.5}$ , however, the HRAPIE experts recommended that this CRF and background rates should be applied to all age groups, given the likelihood of similar or greater effects on MRADs for those aged under 18 and over 64 years.

Ostro and Rothschild (1989) report a mean MRAD of 7.8 days per year among people in employment aged 18–64 years. This is likely to be an underestimate of overall rates in the 18–64 age group because people in employment are on average healthier and better off socioeconomically than those who are unemployed. It is also likely to be a further underestimate of background rates in older people; thus, the extrapolation to other adults is a cautious one.

## 6. Long-term $\text{NO}_2$ exposure

The HRAPIE experts made the recommendations below for use in estimating the health benefits due to  $\text{NO}_2$  per se; for example, in evaluating policies that change  $\text{NO}_2$  concentrations. Coefficients adjusted for other pollutants are therefore recommended for several outcomes. Ideally, this would be complemented by calculating the effect of the relevant other pollutant adjusted for  $\text{NO}_2$  (if the concentration of the other pollutant has also changed as a result of the relevant policy). This is not always possible, but the health benefits for  $\text{NO}_2$  per se would remain correct.

If calculating the overall effects of air pollution – for example, in burden calculations of traffic pollution – an alternative is to use an unadjusted  $\text{NO}_2$  coefficient without including the effect of the other pollutant. This is discussed in detail in the response and rationale given for question C4 in the REVIHAAP project report (WHO, 2013a). General restrictions for using risk coefficients based on multipollutant models are discussed in the introduction to this report (section 1.4).

### 6.1. Effects of long-term $\text{NO}_2$ exposure on all-cause mortality

The recommendation from the response to question C4 in the REVIHAAP project is to include in the cost–benefit analysis the impact of long-term (annual average) exposure to  $\text{NO}_2$  on all-cause (natural) mortality as well as on cardiovascular mortality. The impact calculation should be conducted as Group B\* to contribute to the total effect of the extended set but at the same time avoid potential overlap and double counting of mortality effects from  $\text{PM}_{2.5}$ , which are included in Group A\* analysis.

The HRAPIE experts recommended applying to adult populations (age 30+ years) a linear CRF for all-cause (natural) mortality, corresponding to an RR of 1.055 (95% CI = 1.031, 1.08) per 10  $\mu\text{g}/\text{m}^3$  annual average  $\text{NO}_2$ . The impact should be calculated for levels of  $\text{NO}_2$  above 20  $\mu\text{g}/\text{m}^3$ . Ideally, the annual average would be assessed at a similar spatial scale to that used in the original studies. With a coarser scale the effects of hot spots would be ignored in the cost–benefit analysis, leading to underestimation of the total effects. A CRF for

cardiovascular mortality is not provided as this effect is already included in all-cause mortality.

The recommended risk coefficient is based on the most recently completed meta-analysis of all cohort studies published before January 2013 by Hoek et al. (2013). This considered 11 studies as they were conducted in adult populations of Europe and North America with exposure assessment at the level of the address of residence of the cohort members. The additional inclusion in the meta-analysis of the large American Society Study, based on exposure assessment at the city level and not at the residential address, was associated with only a small decreased overall ES (1.047, 95% CI = 1.024, 1.071).

The annual average NO<sub>2</sub> levels observed in these studies correspond to the range expected for the EU in 2020 under the current legislation scenario (not exceeding 40 µg/m<sup>3</sup> in most areas). No extrapolation beyond the range covered by epidemiological studies on effects of ambient NO<sub>2</sub> is needed.

The recommendation from the REVIHAAP project (question C4) is to use a CRF based on ESs mutually adjusted for PM metrics. When the results of available long-term studies were reviewed, however, only six investigations performed a multipollutant analysis using traffic indicators only (Gehring et al., 2006a; Jerrett et al., 2009b), or specific PM assessment such as total suspended particles (Cao et al., 2011), PM<sub>10</sub> (Hart et al., 2011) or PM<sub>2.5</sub> (Cesaroni et al., 2013; Jerrett et al., 2013) (Table 4). The results were generally similar between single and multipollutant models, with only small changes in the ESs in the multipollutant models (the decrease was in the range 0–33%). In some cases, the CIs of the NO<sub>2</sub> effect were wider after adjustment for the co-pollutant (not in Jerrett et al., 2009b; Cesaroni et al., 2013; Jerrett et al., 2013). Given the results of the multipollutant models, therefore, the CRF is better based on the unadjusted meta-analysis, with the acknowledgement that the resulting estimates of the effects of NO<sub>2</sub> may represent an overestimate in the likely range 0–33%.

The possible threshold above which the NO<sub>2</sub> effect can be estimated has been the focus of few studies. The study by Naess et al. (2007) investigated the CRF between NO<sub>2</sub> and mortality. The study included all inhabitants of Oslo, Norway, aged 51–90 years on 1 January 1992 (n = 1 43 842) with follow-up of deaths from 1992 to 1998. In the youngest age group (51–70 years) risk of death from all causes started to increase at the level of 40 µg/m<sup>3</sup>. In the oldest age group (71–90 years) this increase in risk was linear in the interval 20–60 µg/m<sup>3</sup>. In the study by Cesaroni et al. (2013), investigating the general population of Rome, Italy, (n = 1 265 058) with a follow-up from 2001 to 2010, a statistically significant linear CRF of NO<sub>2</sub> and natural mortality was detected above 20 µg/m<sup>3</sup>. On the basis of these observations, therefore, it is recommended that the NO<sub>2</sub> impact should be calculated for levels above 20 µg/m<sup>3</sup>. This recommendation should be applied to this pollutant–outcome pair only, as evidence is lacking on the possible threshold for quantification of effects for the other outcomes associated with NO<sub>2</sub>.

Findings from the follow-up of the Harvard Six Cities study for PM<sub>2.5</sub> suggest that mortality effects may be partially reversible, over a time period possibly as short as a year (Laden et al., 2006; Lepeule et al., 2012). In the absence of specific information for NO<sub>2</sub>, a similar lag in effects from changing exposure is assumed for NO<sub>2</sub>.

Finally, the recommendation from the REVIHAAP project (question C4) is to include cardiovascular mortality as a “sensitivity” analysis. However, a meta-analytical value is not available for this outcome. On the other hand, as already specified for the PM impact assessment, natural mortality already includes cardiovascular causes of death.

Table 4. ESs for NO<sub>2</sub> from single- and multipollutant models on all-cause (natural) mortality

Reference pollutant	Parameter	All-cause (natural) mortality			% reduction on adjustment	Comments
		Estimate	95% CI			
<b>Gehring et al. (2006a)</b>						
NO <sub>2</sub> single (per 16 µg/m <sup>3</sup> )	Rate ratio	1.19	1.02	1.39	n/a	Women only
With traffic indicator		No change with traffic indicator (data not shown)				
<b>Jerrett et al. (2009b)</b>						
NO <sub>2</sub> single (per 4 ppb)	Rate ratio	1.17	1.00	1.36		Not in Hoek et al. (2013); cohort is from a respiratory clinic
with traffic indicator		1.13	0.97	1.32	24%	
<b>Hart et al. (2011)</b>						
NO <sub>2</sub> single (per 8 ppb)	Percentage increase	8.20	4.50	12.10		Truck drivers
with PM <sub>10</sub> and sulphur dioxide		7.40	2.40	12.50	9.8%	CIs widen
<b>Cao et al. (2011)</b>						
NO <sub>x</sub> single (per 10 µg/m <sup>3</sup> )	Percentage increase	1.50	0.40	2.50		General population
with total suspended particles		1.40	0.30	2.50	6.7%	CIs widen slightly
<b>Cesaroni et al. (2013)</b>						
NO <sub>2</sub> single (per 10 µg/m <sup>3</sup> )	Rate ratio	1.03	1.02	1.04		General population
with PM <sub>2.5</sub>		1.02	1.01	1.03	33%	
with traffic indicator		No change (data not shown)				
<b>Jerrett et al. (2013)</b>						
NO <sub>2</sub> (per 4.1167 ppb)	Rate ratio	1.031	1.008	1.056		General population
With PM <sub>2.5</sub>		1.025	0.997	1.054	19%	

Baseline rates for the total daily number of deaths excluding deaths from external causes should be sourced from the MDB, WHO’s database for use in health impact assessment (WHO, 2013c).

## 6.2. Effects of long-term NO<sub>2</sub> exposure on bronchitic symptoms in asthmatic children

The response and rationale given for question C4 in the REVIHAAP project report (WHO, 2013a) suggests using the report by McConnell et al. (2003) from the Southern California Children’s Health Study. This is the only study of long-term exposure on a respiratory outcome (other than lung function) that includes a coefficient adjusted for other pollutants. The uncertainty in using only one study is acknowledged, although the evidence is supported

by studies of long-term exposure to NO<sub>2</sub> and lung function and by the wider evidence on NO<sub>2</sub> and respiratory outcomes from other types of study.

The effect on bronchitic symptoms (at least three months in a row in the past year) in asthmatic children should be calculated based on an odds ratio of 1.04 (approximately<sup>3</sup> 95% CI = 0.98, 1.11) per 1 ppb NO<sub>2</sub>, equivalent to odds ratio<sup>4</sup> of 1.021 (approximately 95% CI = 0.99, 1.06) per 1 µg/m<sup>3</sup> annual mean NO<sub>2</sub> (McConnell et al., 2003). This coefficient is derived from the two-pollutant model for the yearly deviations in annual average within communities and is adjusted for the effects of OC. The annual mean of 24-hour average NO<sub>2</sub> from community representative monitoring stations or the modelling equivalent should be used in effects estimation.

The background rate of asthmatic children is defined as the percentage prevalence of “asthma ever” in children aged 13–14 years in the EU countries covered in phase three of the ISAAC study (Lai et al., 2009), applied to children aged 5–14 years. Based on this study, the following asthma rates can be applied: 15.8% with sensitivity analysis +/- SD 7.8%<sup>5</sup> for western Europe; 5.1% with sensitivity analysis +/- SD 2.7% for northern and eastern Europe. Alternatively, the prevalence of “asthma ever” by country from Lai et al. (2009) and other sources should be used.

The best measure of asthmatic children, in general terms, is the prevalence of severe wheeze, but that does not match what was used in the original study. Nevertheless, a further alternative analysis using prevalence of severe wheeze as a measure of numbers of asthmatic children is recommended, acknowledging the uncertainty in assuming that the prevalence of bronchitic symptoms is the same in those with severe wheeze (or those with “asthma ever”) as defined in ISAAC, as it is in those with doctor-diagnosed asthma in the Southern California Children’s Health Study. The 12-month prevalence of severe wheeze taken from Lai et al. (2009) is 4.9% for western Europe and 3.5% for northern and eastern Europe.

Uncertainty of the estimation results from both the scarcity of quantitative data on the CRF and the weakness of the background morbidity information. This is quantitative uncertainty in the exact size of the effect rather than conceptual uncertainty as to the causality of the effect. Only one (although well-designed) study from the United States (McConnell et al., 2003) provides the risk coefficient, and there is a need for further work to see if these results are confirmed in other studies. As with many studies of this type, it relies on self-reporting of symptoms, which may vary in reliability (Oksanen et al., 2010). The proportion of asthmatic children is very variable across Europe and there is very little background information on the prevalence of bronchitic symptoms among them, so using the value from the American study is necessary. These additional uncertainties in background morbidity information, which were not reviewed in the REVIHAAP project report, led to the HRAPIE experts placing this pollutant–outcome pair in category B\*. Annex 3 sets out a detailed rationale and discussion of the recommended method.

---

<sup>3</sup> Estimated from graph – see Annex 3.

<sup>4</sup> Approximately the RR for small concentration changes.

<sup>5</sup> Derived from country specific figures in Lai et al. (2009), not population weighted. Range direct from Lai et al. (2009) is 7–28% for western Europe and 2.5–12% in northern and eastern Europe.

## 7. Short-term NO<sub>2</sub> exposure

### 7.1. Effects of short-term NO<sub>2</sub> exposure on all-cause mortality

Responding to question C4, the REVIHAAP project report (WHO, 2013a) recommends estimating the effects of short-term NO<sub>2</sub> exposure on all-cause mortality in all ages on the basis of the results of the APHEA-2 project covering 30 European cities, using a risk coefficient adjusted for at least PM mass. APHEA-2 reported associations between mortality and short-term exposure to NO<sub>2</sub> adjusted for various pollutants, including black smoke and PM<sub>10</sub> (Table 5).

Table 5. Pooled estimates for the increase in mortality associated with an increase of 10 µg/m<sup>3</sup> in daily maximum 1-hour mean NO<sub>2</sub>, adjusting alternatively for the other pollutants

Other pollutant	Total mortality	
	Fixed effects	Random effects
None	0.30 (0.25–0.35)	0.30 (0.22–0.38)
BS	0.33 (0.23–0.42)	0.33 (0.23–0.42)
PM <sub>10</sub>	0.27 (0.20–0.34)	0.27 (0.16–0.38)
SO <sub>2</sub>	0.26 (0.20–0.33)	0.26 (0.18–0.34)
O <sub>3</sub> 8-h	0.34 (0.27–0.40)	0.33 (0.22–0.43)

Source: Samoli et al. (2006); reproduced with permission of the European Respiratory Society.

Notes: Data are presented as percentage increase (95% CI). BS = black smoke; SO<sub>2</sub> = sulphur dioxide; O<sub>3</sub> 8-h = maximum daily 8-hour O<sub>3</sub> concentration.

There is virtually no difference between the estimates from the fixed and random effects models. No evidence of confounding by either particle metric is seen. Adjustment of the association between all-cause mortality and NO<sub>2</sub> for particles leads to a narrow range of central estimates: from 0.27% to 0.33%, around the unadjusted NO<sub>2</sub> estimate of 0.30%. The HRAPIE experts recommended the lower of the estimates for health impact assessment: 0.27% (0.16–0.38%) per 10 µg/m<sup>3</sup> NO<sub>2</sub> (maximum 1 hour) adjusted for PM<sub>10</sub>. This produces more conservative results than quantification exercises that use an estimate adjusted for black smoke. Given the interest in primary combustion particles, the authors note the increase in the NO<sub>2</sub> estimate (to 0.33% (0.23–0.42%)) following adjustment for black smoke (a good indicator of primary combustion particles).

Samoli et al. (2003) assumed a linear CRF between NO<sub>2</sub> daily maximum 1-hour mean and mortality, based on previous analyses from the APHEA-2 project. The median correlation between the daily maximum 1-hour and 24-hour mean NO<sub>2</sub> concentrations was 0.90 (correlation range: 0.80–0.94) and the ratio of 1-hour maximum NO<sub>2</sub> to 24-hour mean was equal to 1.64 in APHEA cities providing both measures of NO<sub>2</sub>. It should be noted, however, that concentrations vary in both time and space and there is therefore variability in the ratios between maximum 1-hour and 24-hour mean concentrations of NO<sub>2</sub>. The analysis should be performed for all NO<sub>2</sub> concentrations.

Baseline rates for the total daily number of deaths excluding deaths from external causes (ICD-10 chapters I–XVIII, codes A–R) should be sourced from the MDB, WHO’s database for use in health impact assessment (WHO, 2013c). This pollutant–outcome pair is recommended for inclusion in Group A\*.

## **7.2. Effects of short-term NO<sub>2</sub> exposure on hospital admissions for respiratory diseases**

Responding to question C4, the REVIHAAP project report (WHO, 2013a) recommends including the effects of short-term NO<sub>2</sub> exposure on hospital admissions for respiratory diseases in all ages in the “core” cost–benefit analysis, suggesting that a risk coefficient adjusted for at least PM mass should be used.

APED was interrogated to identify time-series studies of NO<sub>2</sub> and respiratory hospital admissions for all ages. The relevant studies show that there is heterogeneity in the particle metrics used in two- and multipollutant models (for example, PM<sub>10</sub>, PM<sub>2.5</sub> and black suspended particles<sup>6</sup>) to adjust estimates of NO<sub>2</sub>. In addition, multipollutant models varied in the pollutants other than particles included in the analyses. While this creates little difficulty at the hazard assessment stage, it makes deriving an NO<sub>2</sub> estimate adjusted for particles by meta-analysis difficult. The APHEA-2 project does not contribute to this database since it includes reports only of single-pollutant model estimates of NO<sub>2</sub> for respiratory hospital admissions, and no all-age estimate for this outcome is available (APHEA-2, 2001).

In the light of the above and the REVIHAAP project report observation in the response and rationale to question C2 (WHO, 2013a) that the association between short-term exposure to NO<sub>2</sub> and respiratory hospital admissions is robust to adjustment for co-pollutants, the HRAPIE experts opted to recommend a single-pollutant model estimate, derived by meta-analysis, for use in health impact assessment relating to this outcome.

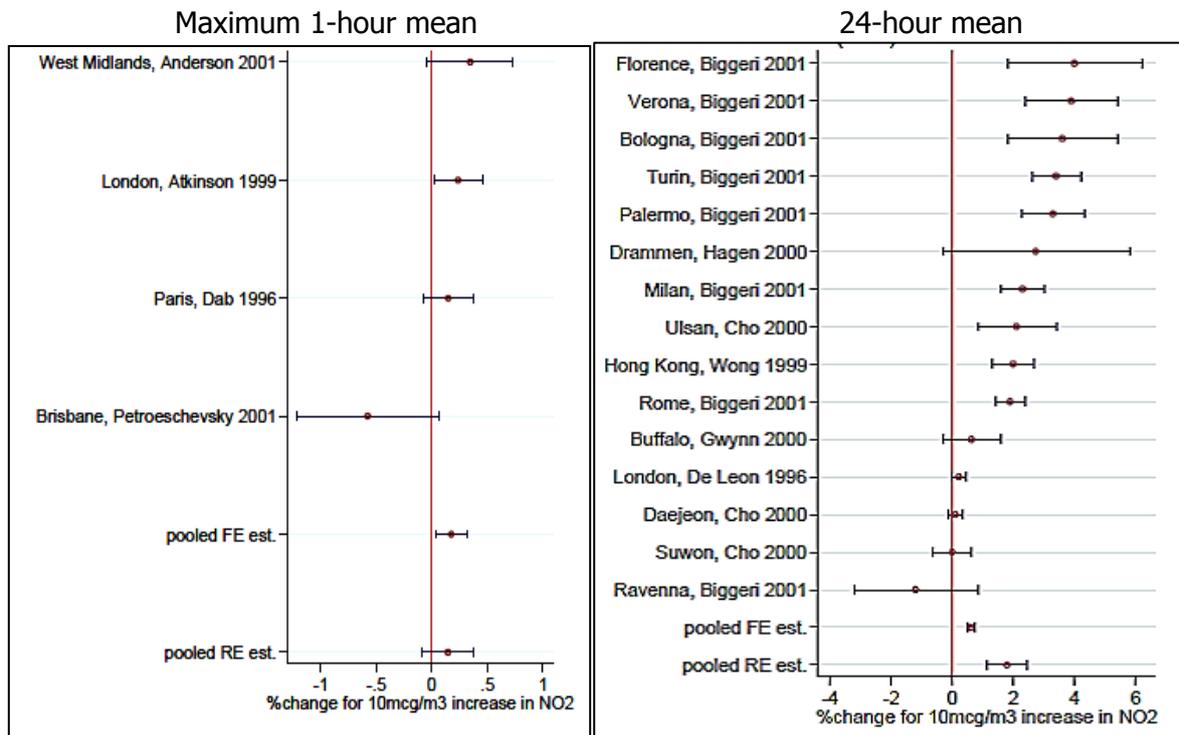
Suitable coefficients were identified from a meta-analysis that used estimates from time-series studies published before 2006 (Anderson et al., 2007). The meta-analysis produced the following risk coefficients for respiratory hospital admissions, all ages: 0.15% (95% CI = -0.08%, 0.38%) per 10 µg/m<sup>3</sup> daily maximum 1-hour average NO<sub>2</sub> and 1.80% (95% CI = 1.15%, 2.45%) per 10 µg/m<sup>3</sup> 24-hour average NO<sub>2</sub>. These coefficients are recommended for use in the cost–benefit analysis, with the 24-hour average as part of Group A\* and the maximum 1-hour mean as an alternative (due to limited data availability). The estimates that formed part of the meta-analyses are shown in Fig. 5 below – the full references relating to the publications cited are available in Anderson et al. (2007). The analysis should be performed for all NO<sub>2</sub> concentrations.

Baseline hospitalization rates for respiratory diseases (ICD-9 codes 460–519; ICD-10 codes J00–J99) can be sourced from the European hospital morbidity database (WHO, 2013f).

---

<sup>6</sup> Black suspended particles are considered an indicator of fine particles less than 2 µm in diameter (Simpson et al., 2005).

Fig. 5. Risk estimates for NO<sub>2</sub> and hospital admissions for respiratory diseases, all ages



Source: Anderson et al. (2007); work funded by and reproduced with permission of the United Kingdom Department of Health Policy Research Programme.

Notes: pooled FE est. = pooled fixed effects estimate; pooled RE est. = pooled random effects estimate.

## References

- Abbey DE et al. (1995a). Estimated long-term ambient concentrations of PM<sub>10</sub> and development of respiratory symptoms in a nonsmoking population. *International Archives for Occupational and Environmental Health*, 50(2):139–152.
- Abbey DE et al. (1995b). Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM<sub>2.5</sub>) and other air pollutants. *Journal of Exposure Analysis and Environmental Epidemiology*, 5(2):137–159.
- Adams PF, Marano MA (1995). Current estimates from the National Health Interview Survey, 1994. *Vital Health and Statistics*, 10(193).
- Ali R et al. (2010). *General Lifestyle Survey 2008: overview report*. Newport, Office of National Statistics (<http://www.ons.gov.uk/ons/rel/ghs/general-lifestyle-survey/2008-report/index.html>, accessed 20 November 2013).
- 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, Favarato G, Atkinson RW (2013). Long-term exposure to outdoor air pollution and the prevalence of asthma: meta-analysis of multi-community prevalence studies. *Air Quality, Atmosphere and Health*, 6(1):57–68.
- APHEA-2 (2001). *Short-term effects of air pollution on health: a European approach to methodology, dose–response assessment and evaluation of public health significance*. (Hard copy of the project report). EC Contract Number ENV4-CT97-0534.
- Atkinson RW et al. (2010). Urban ambient particle metrics and health: a time-series analysis. *Epidemiology*, 21(4):501–511.
- Blanchard M et al. (2008). *Programme de surveillance air et sante – analyse des liens à court terme entre pollution atmosphérique urbaine et mortalité dans neuf villes françaises*. Saint-Maurice, Institut de veille sanitaire ([http://www.invs.sante.fr/publications/2008/psas\\_mortalite/](http://www.invs.sante.fr/publications/2008/psas_mortalite/), accessed 9 May 2013).
- 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.
- Branis M et al. (2010). Association of size-resolved number concentrations of particulate matter with cardiovascular and respiratory hospital admissions and mortality in Prague, Czech Republic. *Inhalation Toxicology*, 22(suppl. 2):21–28.
- Burnett RT et al. (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Environmental Health*, 59(5):228–236.
- 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.
- Carey IM et al. (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *American Journal of Respiratory and Critical Care Medicine*, 187(11):1226–1233.
- 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.
- Cohen AJ et al. (2004). Urban air pollution. In: Ezzati M et al., eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*. Vol. 2. Geneva, World Health Organization: 1353–1434

(<http://www.who.int/publications/cra/chapters/volume2/1353-1434.pdf>, accessed 31 October 2013).

COMEAP (2010). *The mortality effects of long-term exposure to particulate air pollution in the United Kingdom. A report by the Committee on the Medical Effects of Air Pollutants*. Chilton, Health Protection Agency (<http://news.newclear.server279.com/wp-content/uploads/2011/09/comeap-the-mortality-effects-of-long-term-exposure-to-particulate-air-pollution-in-the-uk-2010.pdf>, accessed 15 June 2013).

EC (2013). Legislation: ambient air quality [web site]. Brussels, European Commission (<http://ec.europa.eu/environment/air/legis.htm>, accessed 13 November 2013).

Fung KY, Krewski D (1999). On measurement error adjustment methods in Poisson regression. *Environmetrics*, 10(2):213–224.

Gehring U et al. (2006a). Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. *Epidemiology*, 17(5):545–551.

Gehring U et al. (2006b). Parental education and children’s respiratory and allergic symptoms in the Pollution and the Young (PATY) study. *European Respiratory Journal*, 27(1):95–107.

Gryparis 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.

Hart JE et al. (2011). Long-term ambient multipollutant exposures and mortality. *American Journal of Respiratory and Critical Care Medicine*, 183(1):73–78.

Hoek G, Brunekreef B (1995). Effect of photochemical air pollution on acute respiratory symptoms in children. *American Journal of Respiratory and Critical Care Medicine*, 151(1):27–32.

Hoek G et al. (2012). PM<sub>10</sub>, and children’s respiratory symptoms and lung function in the PATY study. *European Respiratory Journal*, 40(3):538–547.

Hoek G et al. (2013). Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environmental Health*, 12:43.

Holland M (2013). *Implementation of the HRAPIE recommendations for European Air Pollution CBA work: report to the European Commission*. Draft from October 2013.

Host S et al. (2008). Short-term associations between fine and coarse particles and hospital admissions for cardiorespiratory diseases in six French cities. *Occupational and Environmental Medicine*, 65(8):544–551.

Hurley F et al. (2005). *Methodology for the cost–benefit analysis for CAFE. Vol. 2: health impact assessment*. Didcot, AEA Technology Environment ([http://ec.europa.eu/environment/archives/cafe/pdf/cba\\_methodology\\_vol2.pdf](http://ec.europa.eu/environment/archives/cafe/pdf/cba_methodology_vol2.pdf), accessed 19 November 2013).

- Hwang B-F, Lee YL (2010). Air pollution and prevalence of bronchitic symptoms among children in Taiwan. *Chest*, 138(4):956–964.
- IARC (2013). The carcinogenicity of outdoor air pollution. *Lancet Oncology* (doi:10.1016/S1470-2045(13)70487-X).
- IHME (2013). Global Burden of Disease Study 2010 (GBD 2010) – ambient air pollution risk model 1990–2010 [web site]. Seattle, WA, Institute for Health Metrics and Evaluation (<http://ghdx.healthmetricsandevaluation.org/record/global-burden-disease-study-2010-gbd-2010-ambient-air-pollution-risk-model-1990-2010>, accessed 1 November 2013).
- IIASA (2013). *Policy scenarios for the revision of the Thematic Strategy on Air Pollution*. Laxenburg, International Institute for Applied Systems Analysis (TSAP Report, No. 10; <http://ec.europa.eu/environment/air/pdf/review/TSAP-Report-10.pdf>, accessed 14 November 2013).
- Janssen N et al. (2012). *Health effects of black carbon*. Copenhagen, WHO Regional Office for Europe (<http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2012/health-effects-of-black-carbon>, accessed 21 November 2013).
- Jerrett M et al. (2013). Spatial analysis of air pollution and mortality in California. *American Journal of Respiratory and Critical Care Medicine*, 188(5):593–599.
- 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.
- Katsouyanni K et al. (2009). *Air Pollution and Health: a European and North American Approach (APHENA)*. Boston, MA, Health Effects Institute (HEI Research Report 142; <http://pubs.healtheffects.org/getfile.php?u=518>, accessed 20 November 2013).
- Kloog et al. (2013). Long- and short-term exposure to PM<sub>2.5</sub> and mortality: using novel exposure models. *Epidemiology*, 24(4):555–561.
- 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.
- 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 CK et al. (2009). Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*, 64(6):476–483.

- Lepeule J et al. (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six City study from 1974 to 2009. *Environmental Health Perspectives*, 120(7):965–970.
- 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.
- Linares C, Díaz J (2010). Short-term effect of PM<sub>2.5</sub> on daily hospital admissions in Madrid (2003–2005). *International Journal of Environmental Health Research*, 20(2):129–140.
- López-Villarrubia et al. (2010). Air pollution and mortality in the Canary Islands: a time-series analysis. *Environmental Health*, 9:8.
- Mathers CD et al. (2005). Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bulletin of the World Health Organization*, 83(3):171–177.
- 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.
- Migliore E et al. (2009). Respiratory symptoms in children living near busy roads and their relationship to vehicular traffic: results of an Italian multicenter study (SIDRIA 2). *Environmental Health*, 8:27.
- 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.
- Neuberger M, Rabczenko D, Moshhammer H (2007). Extended effects of air pollution on cardiopulmonary mortality in Vienna. *Atmospheric Environment*, 41(38):8549–8556.
- Oksanen T et al. (2010). Self-report as an indicator of incident disease. *Annals of Epidemiology*, 20(7):547–554.
- Ostro BD (1987). Air pollution and morbidity revisited: a specification test. *Journal of Environmental Economics Management*, 14(1):87–98.
- Ostro BD, Rothschild S (1989). Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. *Environmental Research*, 50:238–247.
- Patel SP, Järvelin MR, Little MP (2008). Systematic review of worldwide variations of the prevalence of wheezing symptoms in children. *Environmental Health*, 7:57.
- Perez L et al. (2008). Coarse particles from Saharan dust and daily mortality. *Epidemiology*, 19(6):800–807.

- Perez L et al. (2009). Global goods movement and the local burden of childhood asthma in southern California. *American Journal of Public Health*, 99(suppl. 3):S622–628.
- 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.
- Peters et al. (1997). Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. *European Respiratory Journal*, 10(4):872–879.
- Peters A et al. (2000). Associations between mortality and air pollution in central Europe. *Environmental Health Perspectives*, 108(4):283–287.
- Peters A et al. (2009). *The influence of improved air quality on mortality risks in Erfurt, Germany*. Boston, MA, Health Effects Institute (HEI Research Report 137; <http://pubs.healtheffects.org/getfile.php?u=437>, accessed 19 November 2013).
- Peters JM et al. (1999). A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *American Journal of Respiratory and Critical Care Medicine*, 159(3):760–767.
- 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.
- Rogers DF (2003). Pulmonary mucus: pediatric perspective. *Pediatric Pulmonology*, 36(3):178–188.
- 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. (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. (2013). Associations between fine and coarse particles and mortality in Mediterranean cities: results from the MED-PARTICLES project. *Environmental Health Perspectives*, 121(8):932–938.
- Schindler C et al. (2009). Improvements in PM<sub>10</sub> 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.
- Schikowski T et al. (2013). Ambient air pollution – a cause for COPD? *European Respiratory Journal* (doi:10.1183/09031936.00100112).
- Segala C et al. (1999). Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. *European Respiratory Journal*, 11(3):677–685.

- Simpson R et al. (2005). 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.
- Stafoggia M (2013). Short-term association between fine and coarse particulate matter and hospitalizations in southern Europe – results from the MED-PARTICLES project. *Environmental Health Perspectives*, 121(9):1026–1033.
- Stieb DM et al. (2002). Air pollution and disability days in Toronto: results from the national population health survey. *Environmental Research*, 89(3):210–221.
- van der Zee et al. (1999). Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms. *Occupational and Environmental Medicine*, 56(12):801–812.
- Ward DJ, Ayres JG (2004). Particulate air pollution and panel studies in children: a systematic review. *Occupational and Environmental Medicine*, 61(4):e13.
- Weinmayr G et al. (2010). Short-term effects of PM<sub>10</sub> and NO<sub>2</sub> on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environmental Health Perspectives*, 118:449–457.
- WHO (2001). *Quantification of the health effects of exposure to air pollution: report of a WHO Working Group*. Copenhagen, WHO Regional Office for Europe ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0011/112160/E74256.pdf](http://www.euro.who.int/__data/assets/pdf_file/0011/112160/E74256.pdf), accessed 18 November 2013).
- WHO (2013a). *Review of evidence on health aspects of air pollution – REVIHAAP project: technical report*. Copenhagen, WHO Regional Office for Europe ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0004/193108/REVIHAAP-Final-technical-report.pdf](http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report.pdf), accessed 13 November 2013).
- WHO (2013b). *Health risks of air pollution in Europe – HRAPIE project: new emerging risks to health from air pollution – results from the survey of experts*. Copenhagen, WHO Regional Office for Europe (<http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/health-risks-of-air-pollution-in-europe-hrapie-project.-new-emerging-risks-to-health-from-air-pollution-results-from-the-survey-of-experts>, accessed 13 November 2013).
- WHO (2013c). European mortality database (MDB) [online database]. Copenhagen, WHO Regional Office for Europe (<http://data.euro.who.int/hfamdb/>, accessed 14 November 2013).
- WHO (2013d). European detailed mortality database [online database]. Copenhagen, WHO Regional Office for Europe (<http://data.euro.who.int/dmdb/>, accessed 14 November 2013).
- WHO (2013e). European health for all database [online database]. Copenhagen, WHO Regional Office for Europe (<http://data.euro.who.int/hfad/>, accessed 14 November 2013).

WHO (2013f). European hospital morbidity database [web site]. Copenhagen, WHO Regional Office for Europe (<http://www.euro.who.int/en/what-we-do/data-and-evidence/databases/european-hospital-morbidity-database-hmdb2>, accessed 14 November 2013).

Woodruff TJ, Grillo J, Schoendorf KC (1997). The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. *Environmental Health Perspectives*, 105(6):608–12.

Woodruff TJ, Darrow LA, Parker JD (2008). Air pollution and postneonatal infant mortality in the United States, 1999–2002. *Environmental Health Perspectives*, 116(1):110–15.

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.

## *Annex 1*

# **CONTRIBUTORS TO THE HRAPIE PROJECT**

### ***Scientific Advisory Committee***

This Committee supervises the implementation of the “Health risks of air pollution in Europe – HRAPIE” project and ensures 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
- Nino Künzli, Switzerland
- Xavier Querol, Spain.

### ***Expert authors***

The following experts were involved in the review of evidence providing input to the quantification of the health effects of PM, ground-level O<sub>3</sub> and NO<sub>2</sub> as part of the HRAPIE project, and in drafting the document containing the conclusions of this review:

- Richard Atkinson, United Kingdom
- Francesco Forastiere, Italy
- Fintan Hurley, United Kingdom
- Michal Krzyzanowski, Germany
- Inga Mills, United Kingdom
- Bart Ostro, United States
- Heather Walton, United Kingdom.

### ***External reviewers***

The following experts provided comments on the technical content and clarity of the document, for various sections of the draft material:

- Tom Bellander, Sweden
- Bertil Forsberg, Sweden
- Michael Holland, United Kingdom
- Bryan Hubbel, United States
- Erik Lebret, the Netherlands
- Sarah McGhee, Hong Kong
- Regula Rapp, Switzerland
- Evi Samoli, Greece
- Joel Schwartz, United States
- Dave Stieb, Canada.

### ***Observers at WHO Expert Group meetings***

The following individuals participated in at least one of the WHO meetings organized for the HRAPIE project, in the capacity of observer:

- Markus Amann, International Institute for Applied Systems Analysis (IIASA)
- Arlean Rhode, who provided comments on behalf of Conservation of Clean Air And Water in Europe (CONCAWE)
- André Zuber, European Commission.

### ***WHO Secretariat***

The WHO European Centre for Environment and Health, Bonn, WHO Regional Office for Europe, coordinated the work and development of this publication:

- Svetlana Cincurak
- Marie-Eve Héroux (project leader)
- Elizabet Paunovic
- Helena Shkarubo.

## *Annex 2*

### **EFFECTS OF LONG-TERM NO<sub>2</sub> EXPOSURE ON ASTHMA PREVALENCE IN CHILDREN – QUALITATIVE DESCRIPTION**

This annex provides a qualitative description of the effects of the variation in annual average exposure to NO<sub>2</sub> on asthma prevalence, as the degree to which this is an effect of NO<sub>2</sub> per se is unknown and a meta-analysis of results is not yet available. Some information is given below for use in future calculations of the effect of traffic pollution once the meta-analysis is available, provided estimates of NO<sub>2</sub> modelling are available at an appropriate spatial scale (Table 1). These future quantitative calculations would be in Group B for assessing the effects of NO<sub>2</sub> per se because of the difficulties in identifying which pollutant is responsible, but this uncertainty would not apply if using the CRF to quantify the effects of traffic pollution in general.

Table 1. Recommendations for future calculations of the effect of traffic pollution

<b>Indicator</b>	<b>Recommendation</b>
Population in which effect is calculated	Children aged 5–14 years
CRF	In future this could be based on a meta-analysis in preparation by Anderson, Favarato and Atkinson, but this is best used as an indicator for traffic pollution rather than for NO <sub>2</sub> per se
Exposure metric	Annual average NO <sub>2</sub> from dispersion modelling or land-use regression modelling, or from home or school study monitors at a within-city scale (mostly at the home or school address level)
Baseline rate	Prevalence of asthma defined as the prevalence of current wheeze in the last 12 months in children aged 13–14 years in western Europe and in northern and eastern Europe from the ISAAC study (Lai et al., 2009), applied to children aged 5–14 years
Uncertainties	A good number of studies are available but no multipollutant models and the pollutants are closely correlated; effects are shown at a within-city scale but not at a community area level; baseline asthma prevalence is very variable

The rationale for these recommendations is as follows.

- A range of cross-sectional studies have investigated within-community air pollution exposure contrasts, mostly representative of traffic pollution. These included many positive associations with NO<sub>2</sub>, some of which were statistically significant. An unpublished meta-analysis by Anderson, Favarato and Atkinson is in progress, based on these studies, with air pollution measurements/modelling at a scale likely to pick up variations due to traffic exposure. The results of this meta-analysis could be used in future for quantitative health impact assessment of traffic pollution, but for NO<sub>2</sub> per se calculations it is better to describe the results qualitatively, noting the uncertainty as to whether NO<sub>2</sub> is the responsible pollutant. It should be noted that, whether or not the effect is due to NO<sub>2</sub> per se, the analysis is picking up an effect that is distinct from the effects of PM pollution varying at a broader spatial scale, such as PM<sub>2.5</sub> or PM<sub>10</sub> (given the fact that these pollutants are not associated with asthma prevalence at a community area scale) (Anderson, Favarato and Atkinson, 2013).

- Use of the within-city scale for the exposure metric in estimation of the effects is important as the effects of NO<sub>2</sub> have not been shown at the community area level. It is particularly important for the scale of the modelled concentration used for health impact assessment also to be at a fine spatial scale, as only modelling at this scale picks up traffic pollution contrasts.
- The age range of the children included in the studies included in the meta-analysis was 5–17 years, with the most common age groups centring around about age 10 years. Age 5–14 years is suggested as the affected population as this is likely to match up with other health impact calculations using this age group.
- The prevalence of asthma, defined as current wheeze (in the last 12 months), in children aged 13–14 years in western Europe (including only EU countries) was 14.3%; that in northern and eastern Europe was 9.7% (including non-EU countries) in phase three of the ISAAC study (Lai et al., 2009). (This is closer to the around 6–15% range of baseline prevalence of current asthma defined in various ways in the constituent studies of the meta-analysis than severe wheeze.) Both the western Europe and the northern and eastern Europe rates varied widely between countries (SD 7.0, range 8.1–31.2 and SD 5.0, range 3.4–22.7 respectively: SD based on values for each country, without population weighting). Given the wide variation, baseline wheeze prevalence would ideally be country specific, using information from additional sources (such as Hoek et al., 2012; Gehring et al., 2006b; Patel, Järvelin and Little, 2008) or the constituent studies of the forthcoming meta-analysis by Anderson, Favarato and Atkinson. If data are not available for all the required countries then future calculations of effects of traffic pollution could use the regional values of 14.3% and 9.7% but also include the SD or even the range to make clear the variability in the baseline rate.
- Calculation of the effect should be performed considering that the scaling by concentration needs to be on a log odds basis. (Although this does not differ much from treating the odds ratio as an RR where the numbers affected are small – such as for a small concentration change – it can make a difference at larger concentration changes – for example, in burden calculations.) Thus:
  - the log of the odds ratio per ppb or per µg/m<sup>3</sup> from the meta-analysis, when available, would need to be multiplied by the concentration difference between the annual average for a baseline and for a reduced traffic pollution scenario with NO<sub>2</sub> as an indicator;
  - the exponential of this figure would give the odds ratio for that concentration difference;
  - the odds for the baseline occurrence of wheeze are calculated as the probability divided by one minus the probability: if the prevalence is 14.3%, the odds is  $0.143/(1 - 0.143) = 0.167$ ;
  - the odds ratio for the concentration difference is then multiplied by this baseline to give the new odds of wheeze after the change in pollution;
  - the new odds of wheeze is converted back to a probability (prevalence) =  $\text{new odds}/(1 + \text{new odds})$ ;
  - subtracting the baseline prevalence from the new prevalence gives the change in prevalence of wheeze due to the concentration change from the policy option.

This gives an upper limit in the unlikely case that all the effect is due to NO<sub>2</sub> per se.

- The variability in asthma prevalence between countries is one source of the ES uncertainty (see details in section 6.2 on bronchitic symptoms in asthmatic children). This was for prevalence of “asthma ever” rather than wheeze, as here, but the principles are the same.
- The main uncertainty for calculations intended to quantify the impacts of NO<sub>2</sub> per se is the close correlation between pollutants and the consequent lack of multipollutant models to test which pollutant is responsible for increased risk of asthma near roads. The degree to which NO<sub>2</sub> is responsible for the effect is therefore unknown. The meta-analyses on the prevalence of asthma and wheezing during the study period and on lifetime asthma by Anderson, Favara and Atkinson (2013), both based on nine studies with pollution gradients mainly between communities, did not show any relationship with NO<sub>2</sub> or other pollutants. This emphasizes the importance of matching the scale of the modelling with the studies used to derive the CRF. The difference is probably due to the within-city scale picking up greater exposure contrasts for traffic pollution.

### *Annex 3*

## **BACKGROUND INFORMATION ON ESTIMATION OF EFFECTS OF NO<sub>2</sub> ON BRONCHITIC SYMPTOMS IN ASTHMATIC CHILDREN**

### ***Choice of CRF: within-community or between-communities***

The McConnell et al. (2003) study uses the term “within-community” to describe a coefficient based on the yearly variations around the 4-year mean within a particular community. Note that the same term is used to describe spatial studies based on a within-community spatial scale: this is not what is meant here. The study also includes “between-communities” coefficients based on relating changes in bronchitic symptoms in the past year in asthmatic children to differences in 4-year average NO<sub>2</sub> between the 12 communities studied.

Use of the within-community (yearly variation) associations is recommended for the following reasons:

- the within-community associations were stronger;
- the correlations between NO<sub>2</sub> and other pollutants were lower for the within-community analysis than for the between-communities analysis;
- no consistent between-communities effects were observed in two-pollutant models, but the within-community effects of OC and NO<sub>2</sub> were, in general, not confounded by other pollutants (a key issue for health impact assessment of NO<sub>2</sub> per se);
- using 12 areas and four different years, the yearly variation analysis has greater statistical power.

It should be noted that, while the within-community coefficients are related to temporal variations, the outcome is defined as “daily cough for three months in a row, congestion or phlegm for at least three months in a row or bronchitis” in the past year. It is thus distinct from acute day-to-day variations in symptoms in response to daily variations in pollution. The exact duration of exposure required for the effect is unclear but it is an effect that can be represented by exposure on an annual average basis (see later discussion of the pollution metric).

### ***Choice of CRF: is the within-community coefficient independent of the between-communities coefficient?***

The statistical analysis used in McConnell et al. (2003) was conceptualised as a three-stage regression model of bronchitic symptoms against (i) individual time-dependent covariates such as yearly variations in pollution, (ii) time-independent confounders (such as gender) and (iii) effects of 4-year average pollution.

In essence, the within-community coefficient can be interpreted as being controlled for the effect of the community 4-year average as well as gender, race, smoking and so on. This would suggest that the within-community coefficient can be applied to yearly variations in

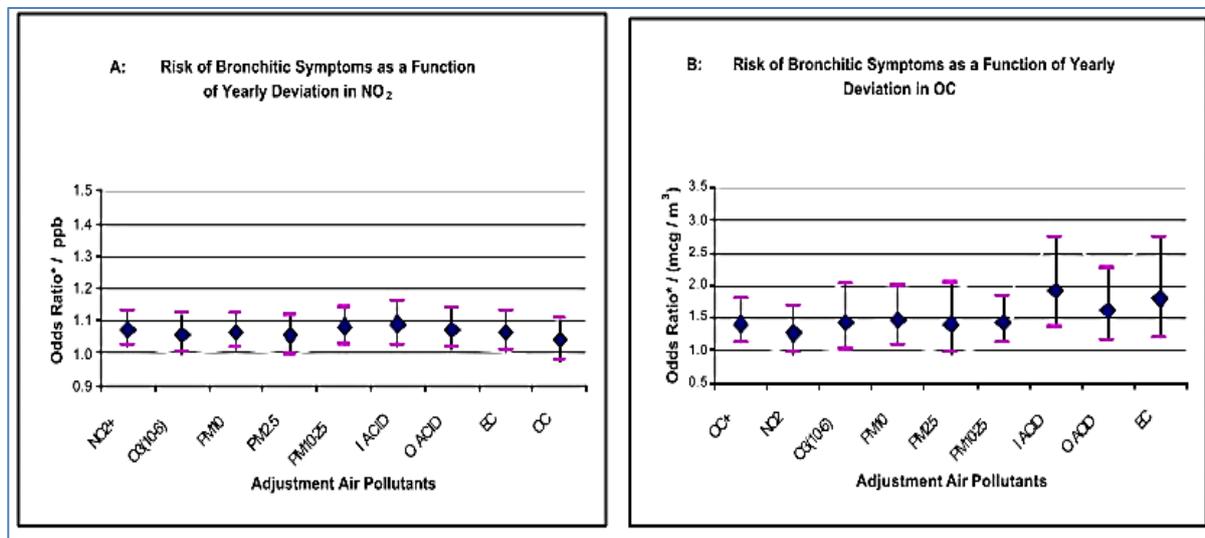
health impact assessment without also having to calculate a 4-year average effect, unless desired. In any case, the 4-year average effect is smaller. The single-pollutant model within-community coefficient for NO<sub>2</sub> has been used in this way in other papers (Künzli et al., 2008; Perez et al., 2009; Perez et al., 2012; Brandt et al., 2012). It should be noted that the between-communities coefficient is in any case small compared with the within-community coefficient.

**Choice of CRF: choice of within-community coefficient adjusted for another coefficient**

The McConnell et al. (2003) study controlled for a wide variety of pollutants. The within-community coefficient for NO<sub>2</sub> was stable to adjustment for O<sub>3</sub> and a whole variety of particle metrics (Fig. 1).

As the aim is to pick out the element of the effect of NO<sub>2</sub> that is independent of possible confounding by other pollutants, a conservative approach was taken to choose the smallest adjusted coefficient. This was the coefficient adjusted for OC, which was the most reduced in size, although it remained positive (and only marginally insignificant) after adjustment. (The OC within-community coefficient was also reduced and became marginally insignificant after adjustment for NO<sub>2</sub>.)

Fig. 1. Odds ratios for the within-community effects of NO<sub>2</sub> and OC, adjusted for each of the other pollutants examined



Source: McConnell et al. (2003), online supplement; reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Official Journal of the American Thoracic Society. Notes: I ACID = inorganic acid; O ACID = organic acid; EC =elemental carbon; OC = organic carbon; O<sub>3</sub>(10–6) = average ozone between 10:00am and 6:00pm.

All odds ratios were adjusted for age, maternal and child’s smoking history, sex and race, and for the between-communities effect of the pollutant indicated. NO<sub>2</sub><sup>+</sup> and OC<sup>+</sup> indicate the within-community odds ratio in a single-pollutant model, adjusted only for the between-communities effects of NO<sub>2</sub> (A) and OC (B) and for personal covariates. All other odds ratios are also for NO<sub>2</sub> (A), or for OC (B), but adjusted in addition for both within-community and between-communities effects of the adjustment pollutant indicated. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

The relevant delta coefficient for NO<sub>2</sub> adjusted for OC was 0.039 (see Table 5 of McConnell et al., 2003). This can be converted to an odds ratio of 1.04, compared with 1.07 per ppb NO<sub>2</sub> for the single-pollutant model. The CIs for the adjusted odds ratio are presented graphically in the online supplement to the paper and are approximately 0.98–1.11 per ppb NO<sub>2</sub> (estimated from Fig. 1 above).

With 1 ppb = 1.88 µg/m<sup>3</sup> NO<sub>2</sub>, the odds ratio of 1.04 (approx. 0.98–1.11) per ppb is equivalent to an odds ratio of 1.02 (approx. 0.99–1.06) per 1 µg/m<sup>3</sup> annual mean NO<sub>2</sub>.

### ***Definition of pollution metric***

The metric used in the study is the annual deviation from the 4-year average of NO<sub>2</sub>, where the annual average is the annual mean of the 24-hour average NO<sub>2</sub> measurement (from measurements every hour) and the 4-year average is the mean of the four annual averages from 1996–1999. The monitoring stations were established to be representative of each community.

The HRAPIE experts consider that the adjusted within-community coefficient based on an annual deviation from a 4-year average could be applied to the difference between an annual average for NO<sub>2</sub> for a baseline scenario and a new annual average for NO<sub>2</sub> subsequent to implementation of a policy. The baseline annual average can be considered conceptually as a long-term average as it is postulated to continue if a policy is not implemented. The policy-induced change in annual average NO<sub>2</sub> would be a small deviation from this in the same way that the annual deviations from one year to another in the original study were small.

### ***Definition of affected population***

The children included in the McConnell et al. (2003) study were aged 9–13 years, but there is no particular reason to suppose that the results would not apply to children a few years outside this age band. As these were asthmatic children, and the nature of asthma/wheeze in very young children differs, an age group such as 5–14 years may be most appropriate.

The study defined asthmatic children as those children who had ever had doctor-diagnosed asthma. McConnell et al. (2003) stated that, in analyses not presented, no effect on bronchitic symptoms was found in non-asthmatic children. The study did not specify what proportion of the asthmatic children used were of the general population but the cross-sectional study done at the start of the Southern California Children’s Health Study (Peters et al., 1999) found that 14.5% of the children were asthmatic, using the same definition as McConnell et al. (2003). This is slightly lower than the 18.3% found in the three American centres in phase three of the ISAAC study (see Table 1 of Lai et al., 2009), but the children in this study were a little older.

The Lai et al. (2009) study provides figures for the prevalence of “asthma ever” in many European countries. While the definition of “asthma ever” is not identical to that used in the Southern California Children’s Health Study (there is no specific mention of doctor diagnosis), it is likely to be quite similar. The results in Lai et al. (2009) are very variable both between countries within a region and between regions. The best approach would be to use country-specific values for “asthma ever”. Not all EU countries are covered in Lai et al. (2009) but it might be possible with further work to obtain figures from national health

examination surveys, or from other published literature, for the missing countries. For example, Hoek et al. (2012) and Gehring et al. (2006b) also give information on prevalence of “asthma ever” (Table 1), including for some countries not included in Lai et al. (2009).

Table 1. Prevalence of “asthma ever”

<b>Study</b>	<b>Prevalence of “asthma ever” from the question “Has a doctor ever diagnosed this child as having asthma?” (Peters et al., 1999), age 12–13 years</b>	<b>Prevalence of “asthma ever” from the question “Have you (has your child) ever had asthma?” (Lai et al., 2009), age 13–14 years</b>	<b>Prevalence of lifetime “asthma ever” from a pooled analysis of several cross-sectional studies of respiratory symptoms. Age ranges varied by dataset, with most studies going up to age 12 years but starting at ages 6, 7, 8 or 9 years (Hoek et al., 2012; Gehring et al., 2006b)</b>
Twelve communities in Southern California (Children’s Health Study)	14.5%		
United States (from three centres) <sup>a</sup> (Lai et al., 2009) or North America (Hoek et al., 2012)		18.3% <sup>b</sup> (SD 1.7%) range 17.3–20.2% (Lai et al., 2009 give an overall figure for the United States of 17.4%)	9.7%
EU countries in phase three of the ISAAC study <sup>c</sup> (Lai et al., 2009), Hoek et al. (2012) or Gehring et al. (2006b)		12.3% (SD 7.6%) range 2.5–28.6%	6.7–22.2% <sup>d</sup>
Western European countries in phase three of the ISAAC study <sup>e</sup> (all EU), Hoek et al. (2012) or Gehring et al. (2006b) <sup>f</sup> (all but Switzerland EU)		16.2% (SD 7.8%) range 7–28.6% (Lai et al., 2009 gives an overall figure for western Europe of 15.8%)	8.1–9%
Northern and eastern European countries in phase three of the ISAAC study (those that are EU), <sup>g</sup> Hoek et al. (2012) or Gehring et al. (2006b)		6.9% (SD 2.7%) range 2.5–12% (Lai et al. (2009) give an overall figure for northern and eastern Europe of 5.1% but this includes non-EU countries and countries as far east as the Russian Federation)	1.9–22.2% <sup>h</sup> (EU only 6.7–22.2%)

<sup>a</sup>: Chapel Hill, Sarasota and Seattle.

<sup>b</sup>: Average, not weighted by population. Also applies to other averages in this column.

<sup>c</sup>: From centres (1–13 per country) based in Austria, Belgium, Bulgaria, the Channel Islands, Estonia, Finland, Germany, Hungary, Ireland, the Isle of Man, Italy, Latvia, Lithuania, Malta (classified as Eastern Mediterranean), the Netherlands, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom.

<sup>d</sup>: Austria, Bulgaria, the Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland and Slovakia.

<sup>e</sup>: From centres (1–13 per country) based in Austria, Belgium, the Channel Islands, Germany, Ireland, the Isle of Man, Italy, the Netherlands, Portugal, Spain and the United Kingdom.

<sup>f</sup>: Austria, Germany, Italy, the Netherlands and Switzerland.

<sup>g</sup>: From centres (1–3 per country) based in Bulgaria, Estonia, Finland, Hungary, Latvia, Lithuania, Poland, Romania and Sweden.

<sup>h</sup>: Bulgaria, the Czech Republic, Hungary, Poland, the Russian Federation and Slovakia (all but the Russian Federation EU).

At the present time, the HRAPIE experts propose use of the western Europe and northern and eastern Europe regional means from Lai et al. (2009). Given the variability, it is also important to include ranges around the mean values. An SD can be derived from the data in Lai et al. (2009), although it is not weighted by population. Another option is to use the range, but this is very wide and it is unlikely that the whole of the region would have the very highest or very lowest prevalence. The relevant values are given below.

- Western Europe: 15.8% with sensitivity analysis +/- SD 7.8%, range 7–28%.
- Northern and eastern Europe: 5.1% with sensitivity analysis +/- SD 2.7%, range 2.5–12%.

The diagnosis of asthma in a child is generally used to indicate that the child has not only current asthmatic symptoms (the asthmatic *state*) but also an underlying asthma *trait*, which implies a chronic condition, whether symptomatic or not at any point of time. The use of the asthma label by doctors is not standardized and varies from physician to physician and from country to country. A report of asthma diagnosis in a questionnaire study does not equate to current asthma symptoms.

To assess health impact it is better to use the prevalence of severe wheeze from questionnaire studies, mostly recollected over the previous 12 months and expressed as a 12-month prevalence, as in ISAAC (Lai et al., 2009). The prevalence of “asthma ever” reported in ISAAC is very likely to overestimate the proportion of children with current asthma symptoms. Use of the prevalence of severe wheeze as a baseline for estimating bronchitic symptoms in asthmatic children based on the McConnell et al. (2003) paper, however, would need to recognize that this estimate was based on children with current doctor-diagnosed asthma-metric, which is not available for Europe. This problem could be resolved if, in fact, doctor-diagnosed asthma in California is closer to the definition of severe wheeze than that of “asthma ever” in ISAAC. Comparison of Peters et al. (1999) and Lai et al. (2009) suggests the prevalence of doctor-diagnosed asthma in the Southern California Children’s Health Study was somewhere between the two ISAAC definitions, but California was not covered in Lai et al (2009).

An alternative analysis using prevalence of severe wheeze rather than prevalence of “asthma ever” as a measure of numbers of asthmatic children is recommended, acknowledging the uncertainty in assuming that the prevalence of bronchitic symptoms is the same in those with severe wheeze (or in those with “asthma ever”), as defined in ISAAC, as it is in those with doctor-diagnosed asthma in the Southern California Children’s Health Study. The 12-month prevalence of severe wheeze taken from Lai et al. (2009) could be used; this is 4.9% for western Europe and 3.5% for northern and eastern Europe.

### ***Baseline rate for bronchitic symptoms in asthmatic children***

The prevalence of bronchitic symptoms (at least three months in a row in the past year) in the asthmatic children in the McConnell et al. (2003) study was 38.7% during the first year of the study. While questions relating to chronic cough and/or phlegm are included in respiratory symptom questionnaires in studies of children, it is uncommon for the results to be stratified by whether or not the children have asthma.

In a cross-sectional study in Taiwan modelled on the Southern California Children’s Health Study, Hwang and Lee (2010) found a similar prevalence of 36.4% bronchitic symptoms in

the last year in asthmatic children aged 12–14 years (mostly 12), defined as those with doctor-diagnosed asthma.

A study in Italy (Migliore et al., 2009) provides data from which it can be calculated that 21.1% of asthmatic children had cough or phlegm for at least four days a week (in the absence of a cold) for one or more months a year. The definition of asthma was wider, however, including one or more wheezing episodes as well as other asthma symptoms as an alternative to doctor-diagnosed asthma, and the children were a combined group aged 6–7 as well as 13–14 years. No other European studies were found on bronchitic symptoms in asthmatic children as opposed to children in general.

Airway mucus hypersecretion is a feature of childhood asthma, has clinical implications and – at least in adults – correlates with bronchial hyper-responsiveness and airway obstruction. Corticosteroids are effective against goblet cell hyperplasia (Rogers, 2003); thus, some of the same issues may apply to variation in bronchitic symptom prevalence in asthmatics, as with other asthma symptoms.

The United States is probably similar to Europe in treatment terms, and in a broad sense – also like Europe – is a country where the prevalence of severe asthma is less than that of “asthma ever”. If instead there was thought to be as high a proportion of untreated asthma as there is in some countries, that might be a specific reason why the prevalence from Southern California might be considered inappropriate to apply in Europe. In fact, no specific reason exists: it is just not known whether it is appropriate or not. It is suggested by the HRAPIE experts that the prevalence in the last year of 38.7% from the Southern California Children’s Health Study is used, with the prevalence in the last year of 21.1% from the study in Italy (using a slightly different definition) as an alternative.

### ***Methodology***

The McConnell et al. (2003) study is analysed by logistic regression and the coefficients expressed as odds ratios: this needs to be taken into account in the calculation. The approach is analogous to that used for calculating effects from odds ratios from panel studies (Hurley et al., 2005).

- 38.7% of children with asthma have bronchitic symptoms in the last year (from McConnell et al., 2003): this implies an odds of  $0.387/(1 - 0.387) = 0.631$ .
- The odds ratio is 1.04 per ppb NO<sub>2</sub>.
- The odds ratio for a difference between a baseline and a reduced scenario (say a difference of 0.5 ppb) =  $\text{EXP}(-(\ln 1.04) \times 0.5) = 0.98$  for a reduced scenario with a 0.5ppb lower annual average for NO<sub>2</sub>. New odds is  $0.98 \times 0.631 = 0.619$ .
- As probability  $0.619/(1 + 0.619) = 0.382$ , a 0.5 ppb lower annual average of NO<sub>2</sub> gives a prevalence that is lower by  $0.387 - 0.382 = 0.5\%$ .

### ***Category A or B***

The response and rationale given for question C4 in the REVIHAAP project report (WHO, 2013a) recommended using bronchitic symptoms in asthmatic children for “core” analysis.

The report noted that a CRF adjusted for other pollutants was available and that there was general support for the plausibility of the effect as a result of toxicological and epidemiological evidence of respiratory effects and other studies of long-term exposure to NO<sub>2</sub> and lung function. It also acknowledged that there was greater uncertainty than for some other endpoints in the core analysis (the recommendation is based on only one study).

The further points discussed in this document refer to quantitative uncertainty in the exact size of the effect rather than conceptual uncertainty as to the causality of the effect. Uncertainty exists for estimating numbers of asthmatic children, but there are data to inform the variability and give a range for the results. Data on the prevalence of bronchitic symptoms in asthmatics are very limited, so this is an important uncertainty.

Ideally, health impact assessment or cost–benefit analysis would be presented categorized according to a range of uncertainties as opposed to just two categories. Given the quantitative uncertainty in the size of the effect due to the evidence on baseline numbers of asthmatic children and baseline rates of bronchitic symptoms in asthmatic children, examined since the REVIHAAP project, the HRAPIE experts concluded that this outcome should be in category B. Bronchitic symptoms in asthmatic children is the main outcome for long-term exposure in terms of the links with the wider respiratory evidence and the separation from other pollutants. It should be emphasized that the Southern California Children’s Health Study and the studies on lung function (see the REVIHAAP project) remain important elements of the evidence for independent effects of long-term exposure to NO<sub>2</sub>, even if the exact size of the effect is uncertain.

## *Annex 4*

### **EFFECTS OF BLACK CARBON EXPOSURE – QUALITATIVE DESCRIPTION**

According to the REVIHAAP project’s conclusions (WHO, 2013a), black carbon could be used in a sensitivity analysis of the cost–benefit analysis. Europe-wide estimates of black carbon exposure are not currently available, however, so the HRAPIE experts do not recommend estimation of black carbon impacts in the EU for the cost–benefit analysis of EU air quality policies. Black carbon can be an additional indicator in evaluating local action aimed at reducing the population’s exposure to combustion PM (for example, from motorized traffic). It should be noted that including both PM<sub>2.5</sub> and black carbon in such analysis may lead to double counting of some of the impacts.

The CRFs for assessment of local black carbon impacts can be retrieved from the WHO evaluation of evidence on the health effects of black carbon (Janssen et al., 2012). A quick search of the literature using PubMed has not revealed any more recent papers that could change the conclusions of this report; nor did the REVIHAAP project’s discussion indicate the need to modify the report’s conclusions.

Local assessment of the effects of black carbon exposure can be based on risk estimates linking long-term exposure to black carbon with all-cause (natural) mortality, as well as short-term exposure to black carbon with hospital admissions for asthma in children and for CVDs (mostly for ages over 65 years).